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(54) NITROGENOUS HETEROCYCLIC COMPOUND.

(57) A nitrogenous heterocyclic compound represented by general formula (I) or a pharmacologically acceptable

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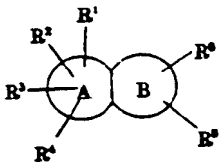
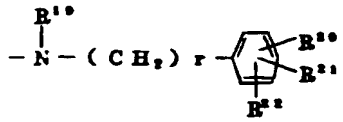
salt thereof, efficacious in treating various ischemic cardiac diseases, wherein ring A represents a benzene, pyridine or cyclohexane ring; ring B represents a pyridine, pyrimidine or imidazole ring; R^1, R^2, R^3 and R^4 represent each hydrogen, halogen, lower alkoxy, etc.; R^5 represents $-NR^{11}R^{12}$ (wherein R^{11} and R^{12} represent each hydrogen, lower alkyl, etc.), etc.; and R^6 represents (a) (wherein R^{19} represents hydrogen, lower alkyl, etc.; R^{20}, R^{21} and R^{22} represent each hydrogen, halogen, hydroxy, etc.; and r represents an integer of 0.1 to 8), etc.



(1)



(a)

[Field of the Invention]

The present invention relates to a nitrogeous heterocyclic compound having an excellent activity as a drug.

[Background of the Invention and Prior Art]

Angina pectoris which is one of ischemic heart diseases has been known as a disease which often attacks the aged. Although nitric and nitrous acid compounds, calcium antagonists and β-blocker have been used as therapeutic agents therefor, the effect of such a therapeutic agent is far insufficient to treat angina pectoris or to prevent the evolution thereof into myocardial infarction. Recently, the age of a patient with angina pectoris has lowered and the symptom thereof has become complicated owing to change in the style of living, stress increased by the complication of society and so forth, so that a new type of more excellent drug has been desired eagerly.

It is believed that cyclic GMP (hereinafter abbreviated to "cGMP") which is one of cyclic nucleotides and is known as an intracellular second messenger participates in the action of the nitric and nitrous acid compounds among the above drugs which are now used. The relaxing effect of cGMP on the smooth muscle of vessel and bronchus is well known. Although the mechanism of action of these drugs are not always apparent, it is generally presumed that the activity of this cGMP results from the acceleration of the synthesis of cGMP which is caused by the activation of guanylate cyclase. However, the above-mentioned drugs exhibit a low bioavailability and a relatively short time of action. Further, it is reported that the drug resistance is induced, which is a problem in a clinical field.

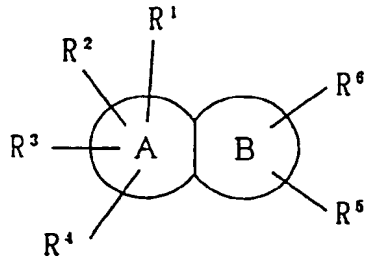
Under these circumstances, the present inventors have started studies to develop a new type of more excellent drug.

That is, the present inventors have paid their attention to cGMP phosphodiesterase (hereinafter abbreviated to "cGMP-PDE")-inhibiting activity and have made extensive studies on compounds having such an activity for many years. As a result of the studies, they have found that a nitrogenous heterocyclic compound which will be described below has such an activity to be efficacious for various ischemic heart diseases and have accomplished the present invention.

Although quinazoline derivatives useful as drugs are included in, e.g., Publication of International Patent Application by Japanese No. 502462/1990, they are different from the compounds of the present invention in respect of both structure and activity.

[Disclosure of the invention]

The present invention provides a nitrogenous heterocyclic compound represented by the following general formula (1) or a pharmacologically acceptable salt thereof:

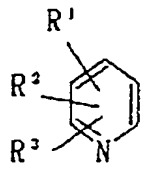


(1)

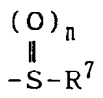
[in formula (1), ring A represents a benzene ring, a pyridine ring or a cyclohexane ring; ring B represents a pyridine ring, a pyrimidine ring or an imidazole ring.

Provided that the ring A and the ring B are combined sharing two atoms and the atoms shared may be either a carbon atom or a nitrogen atom.

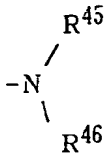
In the case where the ring A is a pyridine ring and that except the case where the ring B shares the nitrogen atom of this pyridine ring to combine therewith, the ring A is represented by



R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a lower alkyl group which may be substituted with a halogen atom, a cycloalkyl group which may be substituted, a lower alkoxy group, a hydroxyalkyl group, a nitro group, a cyano group, an acylamino group, a carboxyl group which may be protected, a group represented by the formula

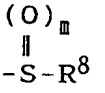


(wherein R^7 represents a lower alkyl group, and n represents 0 or an integer of 1 to 2), or a group represented by the formula

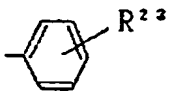


(wherein R^{45} and R^{46}, each of which may be the same or different from each other, represent each a hydrogen atom or a lower alkyl group; or R^{45} and R^{46} can form a ring which may contain another nitrogen atom or oxygen atom together with the nitrogen atom to which they are bonded with the proviso that this ring may be substituted); or, two of R^1, R^2, R^3 and R^4 may together form methylenedioxy, ethylenedioxy or a phenyl ring.

R^5 represents a hydrogen atom, a halogen atom, a hydroxyl group, a hydrazino group, a lower alkyl group, a cycloalkyl group which may be substituted, a lower alkoxy group, a lower alkenyl group, a carboxyalkyl group which may be protected, a carboxyalkenyl group which may be protected, a hydroxyalkyl group, a carboxyl group which may be protected, a group represented by the formula



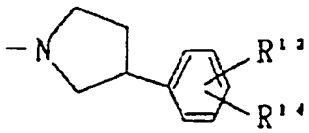
(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula -O-R^9 (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group which may be substituted), a group represented by the formula



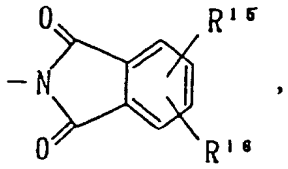
(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl group which

may be substituted, a 1,4-benzdioxylalkyl group which may be substituted, a group represented by the formula $-C(R^{24})=X$ [wherein X represents an oxygen atom, a sulfur atom or a group represented by the formula $=N-R^{10}$ (wherein R^{10} represents a hydroxyl group, a cyano group or a carboxyalkyloxy group which may be protected); and R^{24} represents a hydrogen atom or a lower alkyl group], or a group represented by the formula $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, an aminoalkyl group, a carboxyalkyl group which may be protected, an alkylcarbamoyl group, a carboxyalkylcarbamoyl group which may be protected, a heteroarylalkyl group which may be substituted, a 1,3-benzoxolylalkyl group or a 1,4-benzdioxylalkyl group; or, further, R^{11} and R^{12} can form a ring which may contain another nitrogen atom or oxygen atom together with a nitrogen atom to which they are bonded with the proviso that this ring may be substituted).

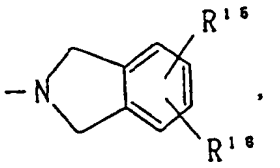
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



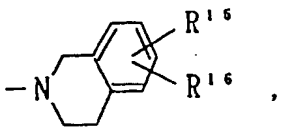
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



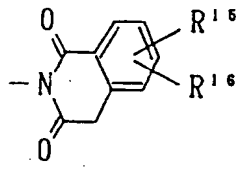
a group represented by the formula



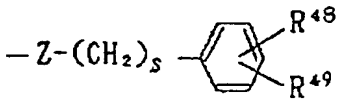
a group represented by the formula



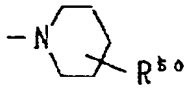
a group represented by the formula



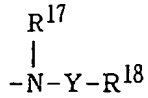
(in these formulas, R^{15} and R^{16}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidne-4-spiro-2'-dioxan-1-yl group, a group represented by the formula



(wherein R^{48} and R^{49}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{48} and R^{49} may together form methylenedioxy or ethylenedioxy; and Z represents a sulfur atom or an oxygen atom), a group represented by the formula

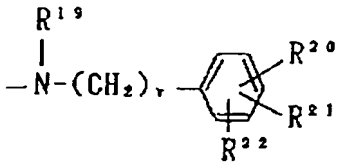


(wherein R^{50} represents a hydroxyl group, a halogen atom, a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a cyano group, a hydroxyalkyl group or a carboxyalkyl group), a group represented bythe formula



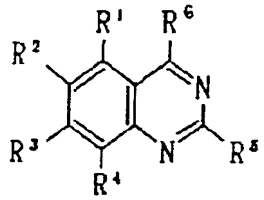
[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented by the formula

further, in the group represented by the formula $-(CH_2)_q-$, when q is an integer of 1 to 8, each carbon atom may have 1 to 2 substituent(s); and R^{18} represents a hydrogen atom, a hydroxyl group, a carboxyl group which may be protected, a cyano group, an acyl group, a heteroaryl group which may be substituted or a cycloalkyl group which may be substituted], or a group represented by the formula



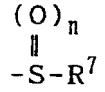
(wherein R^{19} represents a hydrogen atom, a lower alkyl group, a lower alkoxyalkyl group, an acyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; R^{20}, R^{21} and R^{22}, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a lower alkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a lower alkenyl group, an acyl group, an acylamino group, an alkylsulfonylamino group, a hydroxyiminoalkyl group, an alkyloxycarbonylamino group, an alkyloxycarbonyloxy group or a heteroaryl group which may be substituted; or, further, two of R^{20}, R^{21} and R^{22} may together form a saturated or unsaturated ring which may contain a nitrogen atom, a sulfur atom or an oxygen atom; and r represents 0 or an integer of 1 to 8)].

The quinazoline derivative represented by the following formula (I) or the pharmacologically acceptable salt thereof can be cited as one of the preferred embodiments of the nitrogenous heterocyclic compound represented by the formula (1) described above or the pharmacologically acceptable salt thereof:



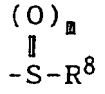
(I)

[in formula (I), R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group, a cyano group, an acylamino group, a carboxyl group which may be protected or a group represented by the formula

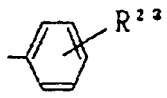


(wherein R^7 represents a lower alkyl group; and n represents 0 or an integer of 1 to 2), or two of R^1, R^2, R^3 and R^4 may together form methylenedioxy, ethylenedioxy or a phenyl ring.

R^5 represents a hydrogen atom, a halogen atom, a hydroxyl group, a hydrazino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a carboxyalkyl group which may be protected, a carboxyalkenyl group which may be protected, a hydroxyalkyl group, a carboxyl group which may be protected, a group represented by the formula

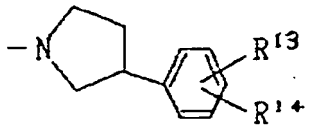


(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula -O-R^9 (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group), a group represented by the formula

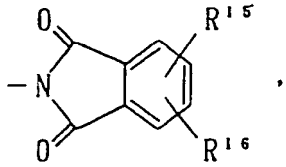


(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl group which may be substituted, a 1,4-benzdioxylalkyl group which may be substituted, a group represented by the formula $-C(R^{24})=X$ [wherein X represents an oxygen atom or a group represented by the formula $=N-R^{10}$ - (wherein R^{10} represents a hydroxyl group or a carboxyalkyloxy group which may be protected); and R^{24} represents a hydrogen atom or a lower alkyl group], or a group represented by the formula $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, an aminoalkyl group, a carboxyalkyl group which may be protected, an alkylcarbamoyl group, a 1,3-benzoxolylalkyl group or a 1,4-benzdioxylalkyl group; or, further, R^{11} and R^{12} can form a ring which may contain another nitrogen atom or oxygen atom together with a nitrogen atom to which they are bonded with the proviso that this ring may be substituted).

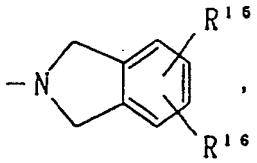
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



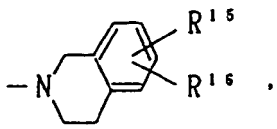
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



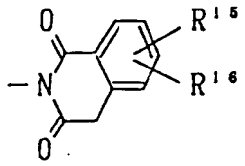
a group represented by the formula



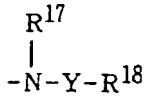
a group represented by the formula



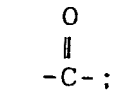
a group represented by the formula



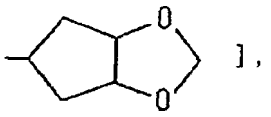
(in these formulas, R^{15} and R^{16} represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidne-4-spiro-2'-dioxan-1-yl group or a group represented by the formula



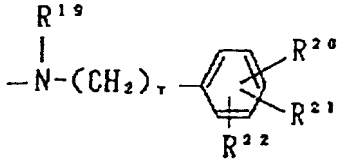
[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented by the formula



further, in the group represented by the formula $-(CH_2)_q-$, when q is an integer of 1 to 8, each carbon atom may have 1 to 2 substituent(s); and R^{18} represents a hydrogen atom, a hydroxyl group, a carboxyl group which may be protected, a cyano group, an acyl group, a heteroaryl group which may be substituted or a group represented by the formula



or a group represented by the formula



(wherein R^{19} represents a hydrogen atom, a lower alkyl group, a lower alkoxyalkyl group, an acyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; R^{20}, R^{21} and R^{22}, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a lower alkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a lower alkenyl group, an acyl group, an acylamino group, an alkylsulfonylamino group, a hydroxyiminoalkyl group, an alkyloxycarbonylamino group, an alkyloxycarbonyloxy group or a heteroaryl group which may be substituted; or, two of R^{20}, R^{21} and R^{22} may together form a saturated or unsaturated ring which may contain a nitrogen atom, a sulfur atom or an oxygen atom; and r represents 0 or an integer of 1 to 8)].

The present invention also provides a preventive or therapeutic agent for diseases for which phosphodiesterase-inhibiting action is efficacious, especially for which cyclic-GMP phosphodiesterase-inhibiting action is efficacious, which contains a nitrogenous heterocyclic compound or a pharmacologically acceptable salt thereof described above as the active ingredient.

As diseases described above, ischemic heart diseases, concretely angina pectoris, hypertension, heart failure and asthma, are cited.

Furthermore, the present invention provides a drug composition comprising a nitrogenous heterocyclic compound and/or a pharmacologically acceptable salt thereof described above and a pharmacologically acceptable filler.

The present invention provides a use of a nitrogenous heterocyclic compound or a pharmacologically acceptable salt thereof to prepare a therapeutic agent for diseases for which phosphodiesterage-inhibiting action is efficacious, and a treating method for a disease which comprises administering a therapeutic effective amount of a nitrogenous heterocyclic compound and/or a pharmacologically acceptable salt thereof to a patient suffering from a disease for which phosphodiesterase-inhibiting action is efficacious.

The lower alkyl group defined with respect to R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{45}, R^{46}, R^{48}, R^{49} and R^{50} in the above definition of the compound (1) according to the present invention is a straight-chain or branched alkyl group having 1 to 8 carbon atoms and examples thereof include methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group (amyl group), neopentyl group, tert-pentyl group, 2-methylbutyl group, 3-methylbutyl group, 1,2-dimethylpropyl group, hexyl group, isohexyl group, 1-methylpentyl group, 2-methylpentyl group, 3-methylpentyl group, 2,2-dimethylbutyl group, 2,3-dimethylbutyl group, 3,3-dimethylbutyl group, 2-ethylbutyl group, 1,1,2-trimethylpropyl group, 1,2,2-trimethylpropyl group, 1-ethyl-1-methylpropyl group, 1-ethyl-2-methylpropyl group, heptyl group and octyl group. Among these groups, methyl group, ethyl group, propyl group and isopropyl group are cited as preferable ones. Among these groups, methyl group and ethyl group are cited as still preferable ones.

In these lower alkyl groups, a carbon atom at its terminal may be represented by a sulfonic acid group ($-SO_3H$) or a group represented by the formula $-ONO_2$. Furthermore, the sulfonic acid group may form a salt such as groups represented by the formulas $-SO_3Na$ and $-SO_3K$.

The lower alkyl group which may be substituted with a halogen atom used in the definition of R^1, R^2, R^3 and R^4 refers to a lower alkyl group described above in which one or two or more hydrogen atoms may be replaced by halogen atom(s).

The lower alkoxy group defined with respect to R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{14}, R^{15}, R^{16}, R^{20}, R^{21}, R^{22}, R^{23}, R^{48}, R^{49} and R^{50} is a straight-chain or branched alkoxy group having 1 to 8 carbon atoms and examples thereof include methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, 2-methylbutoxy group, 2,3-dimethylbutoxy group and hexyloxy group. Among these groups, methoxy group and ethoxy group are cited as preferable ones.

The lower alkenyl group defined with respect to R^5, R^6, R^{20}, R^{21} and R^{22} is one derived from the above-mentioned lower alkyl group and examples thereof include ethylene group, propylene group, butylene group and isobutylene group.

The hydroxyalkyl group defined with respect to R^1, R^2, R^3, R^4, R^5, R^{11}, R^{12}, R^{17}, R^{19}, R^{23} and R^{50} is one derived from the above-mentioned lower alkyl group.

The hydroxyalkyl group which may be protected used in the definition of R^9 refers to a hydroxyalkyl group wherein the hydroxyl group is protected with, for example, nitro group, a lower alkyl group as described above such as methyl group and ethyl group, an acyl group such as acetyl group, propionyl group, butyroyl group, pivaloyl group and nicotinoyl group or other group which may have a c-GMP PDE-inhibitory activity. The nitrogenous heterocyclic compound thus protected according to the present invention exhibits an effect as a drug after being deprotected the protective group in vivo or as such.

The acyl group defined with respect to R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} is one derived from an aliphatic one, an aromatic one or a heterocycle and examples thereof include lower alkanoyl groups such as formyl group, acetyl group, propionyl group, butyryl group, valeryl group, isovaleryl group and pivaloyl group; aroyl groups such as benzoyl group, toluoyl group and naphthoyl group; and heteroaroyl groups such as furoyl group, nicotinoyl group and isonicotinoyl group. Among these groups, formyl group, acetyl group and benzoyl group are cited as preferable ones.

The carboxyl-protective group defined with respect to R^1, R^2, R^3, R^4, R^5, R^{18} and R^{50} includes lower alkyl groups such as methyl group, ethyl group and t-butyl group; lower alkyl groups substituted with a phenyl group which may have a substituent, such as p-methoxybenzyl group, p-nitrobenzyl group, 3,4-dimethoxybenzyl group, diphenylmethyl group, trityl group and phenethyl group; halogenated lower alkyl

groups such as 2,2,2-trichloroethyl group and 2-iodoethyl group; lower alkanoyloxy lower alkyl groups such as pivaloyloxymethyl group, acetoxymethyl group, propionyloxymethyl group, butyryloxymethyl group, valeryloxymethyl group, 1-acetoxyethyl group, 2-acetoxyethyl group, 1-pivaloyloxyethyl group and 2-pivaloyloxyethyl group; higher alkanoyloxy lower alkyl groups such as palmitoyloxyethyl group, heptadecanoyloxymethyl group and 1-palmitoyloxyethyl group; lower alkoxy-carbonyloxy lower alkyl groups such as methoxycarbonyloxymethyl group, 1-butoxycarbonyloxyethyl group and 1-(isopropoxycarbonyloxy)-ethyl group; carboxy lower alkyl groups such as carboxymethyl group and 2-carboxyethyl group; heterocyclic groups such as 3-phthalidyl group; benzoyloxy lower alkyl groups which may have a substituent, such as 4-glycyloxybenzoyloxymethyl group and 4-[N-(t-butoxycarbonyl)glycyloxy]-benzoyloxymethyl group; (substituted dioxolene) lower alkyl groups such as (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group; cycloalkyl-substituted lower alkanoyloxy lower alkyl groups such as 1-cyclohexylacetyloxyethyl group; and cycloalkyloxycarbonyloxy lower alkyl groups such as 1-cyclohexyloxycarbonyloxyethyl group.

Further, the protected carboxyl group also includes various acid amides groups. That is, the protected carboxyl group may be any one, so far as it can be deprotected in vivo to give a carboxyl group. The nitrogenous heterocyclic compound thus protected according to the present invention exhibits an effect as a drug after being deprotected the protective group in vivo or as such.

Although the cycloalkyl group which may be substituted used in the definition of R^1, R^2, R^3, R^4, R^5 and R^{18} refers to one having 3 to 8 carbon atoms, those having 3 to 6 carbon atoms are preferable.

The heteroaryl group constituting the heteroaryl group which may be substituted defined with respect to R^5, R^{18}, R^{20}, R^{21} and R^{22} is a 5- to 7-membered monocyclic group or a condensed heterocyclic group each containing one to two oxygen atom(s), nitrogen atom(s) or sulfur atom(s) as the heteroatom(s) and examples thereof include furyl group, pyridyl group, thienyl group, imidazolyl group, quinazolyl group and benzimidazolyl group.

The heteroaryl group constituting the heteroarylalkyl group which may be substituted defined with respect to R^{11} and R^{12} refers to any of the heteroaryl groups described above. Further, the alkyl group constituting the heteroaryl group refers to any of the lower alkyl groups described above.

"$R^{11(45)}$ and $R^{12(46)}$ and the nitrogen atom to which both groups are bonded may together form a ring which may contain another nitrogen atom or an oxygen atom" described in the definition of R^{11} and R^{12}, and R^{45} and R^{46} refers to piperidino group, piperazino group and morpholino group as specific examples. Further, the substituent with which the ring may be substituted includes hydroxyl group; halogen atoms such as chlorine atom, fluorine atom, bromine atom and iodine atom; lower alkyl groups such as methyl, ethyl and t-butyl; lower alkoxy groups such as methoxy, ethoxy and t-butoxy; cyano groups; carboxyl groups which may be protected; hydroxyalkyl groups; carboxyalkyl groups; heteroaryl groups such as tetrazolyl group; and so on. The ring may have one to two substituents described above.

The substituent constituting the "heteroaryl group which may be substituted" contained in the definition of R^5, R^{18}, R^{20}, R^{21} and R^{22}, the "phenylalkyloxy group which may be substituted" contained in the definition of R^5, the "1,3-benzdioxolyl group which may be substituted, 1,4-benzdioxyl group which may be substituted, 1,3-benzdioxolylalkyl group which may be substituted or 1,4-benzdioxylalkyl group which may be substituted" contained in the definition of R^5, the "benzyl group which may be substituted" defined with respect to R^9 and the "heteroarylalkyl group which may be substituted" defined with respect to R^{11} and R^{12} includes, for example, hydroxyl group; nitro group; halogen atoms such as chlorine atom, fluorine atom, bromine atom and iodine atom; lower alkyl groups such as methyl, ethyl and t-butyl; lower alkoxy groups such as methoxy, ethoxy and t-butoxy; carboxyl groups which may be protected; hydroxyalkyl groups; carboxyalkyl groups; tetrazolyl group; and so on.

Further, the substituent constituting the "group represented by the formula $-(CH_2)_q-$ wherein each carbon may have one to two substituents when q is an integer of 1 to 8" contained in the definition of Y includes the same substituents as those described above.

Although the acylamino group defined with respect to R^1, R^2, R^3, R^4, R^{20}, R^{21} and R^{22} refers to an amino group wherein an acyl group(s) as described above is(are) bonded to the nitrogen atom of the amino group, i.e., monoacylamino group or diacylamino group, the monoacylamino group is preferred.

The halogen atom defined with respect to R^1, R^2, R^3, R^4, R^5, R^6, R^{20}, R^{21}, R^{22} and R^{50} includes fluorine atom, chlorine atom, bromine atom and iodine atom.

The carboxylalkyl group which may be protected defined with respect to R^5, R^9, R^{10}, R^{11}, R^{12}, R^{17} and R^{19} is a carboxyalkyl group wherein the carboxyl group may be protected with the carboxyl-protective group described above. Further, the carboxy group(s) in this carboxyalkyl group may be bonded to any and one to two carbon atom(s) of the lower alkyl group as described above.

The carboxyalkenyl group which may be protected defined with respect to R^5 refers to a carboxyalkenyl group wherein the carboxyl group is protected with the carboxyl-protective group described above. Further, the carboxy group(s) in this carboxyalkenyl group may be bonded to any and one to two carbon atom(s) of the lower alkyl group as described above.

The lower alkoxyalkyl group defined with respect to R^{17}, R^{19}, R^{20}, R^{21} and R^{22} is one derived from the above-mentioned lower alkyl group and examples thereof include methoxymethyl group, methoxyethyl group, methoxybutyl group and ethoxyethyl group.

The aminoalkyl group defined with respect to R^{11} and R^{12} refers to a lower alkyl group as described above wherein an amino group is bonded to any of the carbon atoms constituting the lower alkyl group.

The alkylcarbamoyl group defined with respect to R^{11} and R^{12} refers to one derived from the above-mentioned lower alkyl group.

The carboxyalkylcarbamoyl group which may be protected used in the definition of R^{11} and R^{12} refers to any of the alkylcarbamoyl groups described above which has a carboxyl group, which may be protected, bonded to any carbon atom of the alkyl.

The alkylsulfonylamino group defined with respect to R^{20}, R^{21} and R^{22} refers to one derived from the above-mentioned lower alkyl group.

The hydroxyiminoalkyl group defined with respect to R^{20}, R^{21} and R^{22} is a lower alkyl group as described above wherein a hydroxyimino group is bonded to any of the carbon atoms constituting the lower alkyl group.

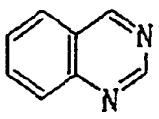
Although the alkyloxycarbonylamino group defined with respect to R^{20}, R^{21} and R^{22} is an amino group wherein the nitrogen atom of the amino group is mono-or disubstituted with an alkyloxycarbonyl derived from the above-mentioned lower alkyl group, the mono-substituted alkyloxycarbonylamino group is preferable.

The alkyloxycarbonyloxy group defined with respect to R^{20}, R^{21} and R^{22} refers to a group wherein an alkyloxycarbonyl derived from the above-mentioned lower alkyl group is bonded to an oxygen atom.

The hydroxyalkyloxy group defined with respect to R^{23} refers to one derived from the hydroxyalkyl group described above.

In the compounds of the present invention, a ring part of a bicyclic skeleton wherein the ring A and ring B are combined or a three or more ring skeleton when two of the substituents on the ring A together form a ring, is formed. Among these, desirable examples are as follows:

a)



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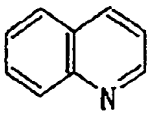
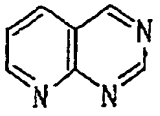
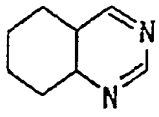


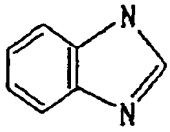
c)



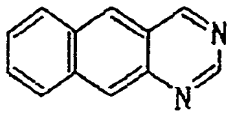
d)



e)



f)



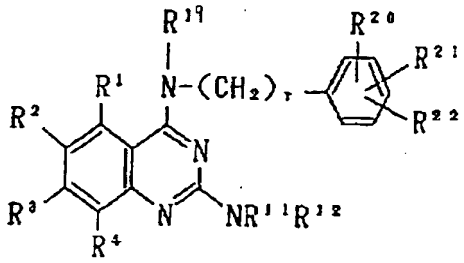
Among these, a), b), c) and e) are cited as more desirable ones and a), b) and c) are cited as more desirable ones. Most desirable one is a).

The pharmacologically acceptable salt includes inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts such as acetate, maleate, tartrate, methanesulfonate, benzenesulfonate and toluenesulfonate; and amino acid salts such as argininate, aspartate and glutamate. Further, some of the compounds may form metal salts such as Na, K, Ca or Mg, and the pharmacologically acceptable salt of the present invention also includes these metal salts.

Although the compound of the present invention may be present as various isomers including geometrical isomers, i.e., cis-isomer and trans-isomer, and optical isomers, i.e., d-isomer and l-isomer depending upon the kinds and combination of the substituents, it is needless to say that the compounds of the present invention includes all of the isomers.

Preferable specific examples of the compound of the present invention will now be described in order to facilitate the understanding of the present invention, though it is needless to say that the compounds of the present invention are not limited to these examples.

The most desirable specific examples of the compound include compounds represented by the following general formula (A) and pharmacologically acceptable salts thereof:



(A)

[in general formula (A), R^1, R^2, R^3, R^4, R^{11}, R^{12}, R^{19}, R^{20}, R^{21}, R^{22} and r are the same as those in general formula (1)].

As R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, hydrogen atom, a halogen atom and cyano group are preferable and, among them, hydrogen atom, cyano group and chlorine atom are still preferable.

To enter into details with respect to the combination of R^1, R^2, R^3 and R^4, it is desirable that one of R^1, R^2, R^3 and R^4 is cyano group or chlorine atom and the others are hydrogen atoms and, among them, it is most desirable that R^2 is cyano group or chlorine atom and R^1, R^3 and R^4 are hydrogen atoms.

As R^{11} and R^{12}, each of which may be the same or different from each other, hydrogen atom, a lower alkyl group and a carboxyalkyl group which may be protected are preferable and, among these, hydrogen atom, methyl group and 3-carboxypropyl group are preferable.

Further, it is most desirable that R^{11} and R^{12}, together with the nitrogen atom to which they are bonded, form a ring which may be substituted, and among them, a piperidine ring is most desirable. It is still preferable that this ring is substituted with a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a hydroxyl group, a halogen atom, a hydroxyalkyl group or a carboxyalkyl group, and among them, a carboxyl group which may be protected is most preferable.

R^{19} is preferably a hydrogen atom or a lower alkyl group such as methyl group and ethyl group, particularly preferably a hydrogen atom.

r is desirably 0, 1 or 2, most desirably 1.

As R^{20}, R^{21} and R^{22}, a hydrogen atom, a lower alkyl group, a lower alkoxy group and a halogen atom are preferable, or it is preferable that two of R^{20}, R^{21} and R^{22} together form methylenedioxy or ethylenedioxy.

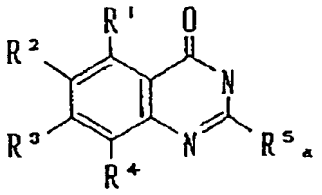
[Preparation process]

Representative processes for the preparation of the compound according to the present invention will now be described below.

Though compounds having a quinazoline skelton are mainly described in the following explanation, the following explanation can be applied for compounds having a skelton other than the quinazoline skelton.

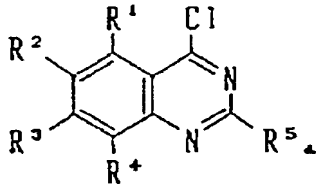
Preparation process 1

When R^5 is a hydrogen atom, a halogen atom or a group selected from among those which are directly bonded to the quinazoline skeleton through a carbon atom in the general formula (I), a compound represented by the general formula (I) can also be prepared by the following process:



(II)

phosphorus oxychloride or
phosphorus oxychloride + phosphorus pentachloride / heating



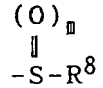
(III)

(in a series of formulas, $R^5{}_a$ is a hydrogen atom, a halogen atom or a group selected from among those which are directly bonded to the quinazoline skeleton through a carbon atom in R^5 described above; and R^1, R^2, R^3 and R^4 are each as defined above.

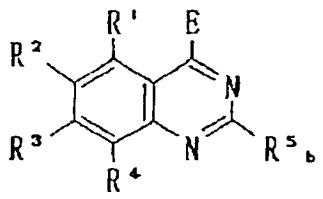
That is, this process is one for preparing a quinazoline derivative represented by the general formula (III) by reacting a quinazoline derivative represented by the general formula (II) with phosphorus oxychloride or by reacting it with phosphorus oxychloride in the presence of phosphorus pentachloride under heating.

Preparation process 2

When R^5 is a group selected from among a hydrogen atom, a halogen atom, a group represented by the formula

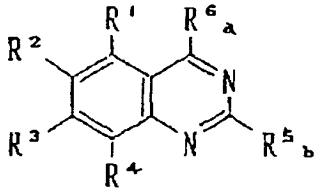


(wherein R^8 and m are each as defined above), a group represented by the formula -O-R^9 (wherein R^9 is as defined above), a heteroaryl group which may be substituted and a group which is directly bonded to the ring through a carbon atom (for example, a lower alkyl group, a carboxyl group which may be protected, a 1,3-benzodioxolyl group which may be substituted, a 1,4-benzodioxyl group which may be substituted, a 1,3-benzodioxolylalkyl group which may be substituted and a 1,4-benzodioxylalkyl group which may be substituted); and R^6 is a group selected from among those defined above with respect to R^6 except a hydrogen atom, halogen atoms and lower alkyl groups in the general formula (I), a compound represented by the general formula (I) can be prepared by the following process:



(IV)

(base) | H—R$^{6}_{a}$ or its salt (VI)



(V)

[in a series of formulas, R^1, R^2, R^3 and R^4 are each as defined above; $R^5{}_b$ represents a group selected from among a hydrogen atom, a halogen atom, a group represented by the formula

(wherein R^8 and m are each as defined above), a group represented by the formula -O-R^9 (wherein R^9 is as defined above), a heteroaryl group which may be substituted and a group which is directly bonded to the ring through a carbon atom (for example, a lower alkyl group, a carboxyl group which may be protected, a 1,3-benzodioxolyl group which may be substituted, a 1,4-benzodioxyl group which may be substituted, a 1,3-benzodioxolylalkyl group which may be substituted and a 1,4-benzodioxylalkyl group which may be substituted); $R^6{}_a$ represents a group selected from among those defined above with respect to R^5 except a hydrogen atom, halogen atoms and lower alkyl groups; and E represents an eliminable group].

That is, this process is one for preparing an objective compound (V) by condensing a quinazoline derivative represented by the general formula (IV) with a compound represented by the general formula (VI).

The eliminable group represented by E in the formula includes halogen atoms and alkoxy groups.

This process may be conducted in the presence of a base at need.

The base includes organic bases such as triethylamine, pyridine and diisopropylethylamine; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium hydroxide and sodium hydride; and alkoxides such as sodium methoxide and potassium t-butoxide.

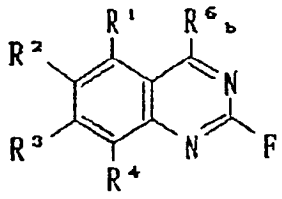
As the reaction solvent, every solvent which is inert to the reaction can be used and examples thereof include ethanol, isopropyl alcohol, tetrahydrofuran, dimethylformamide and dimethyl sulfoxide. This process can be conducted even in the absence of any solvent in some cases.

The reaction temperature preferably ranges from -20 to 300 °C.

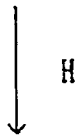
Preparation process 3

When R^5 is a group selected from among those defined above with respect to R^5 except a hydrogen atom, halogen atoms and groups which are directly bonded to the quinazoline skeleton through a carbon atom; and R^6 is a group selected from among those defined above with respect to R^6 except halogen atoms in the general formula (I), a compound represented by the general formula (I) can be prepared by the

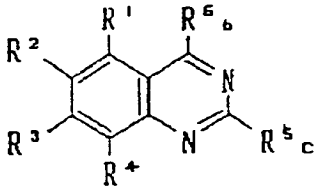
following process:



(VII)



H — $R^5{}_c$ or its salt (IX)



(VIII)

(in a series of formulas, R^1, R^2, R^3 and R^4 are each as defined above; $R^5{}_c$ is a group selected from among those defined above with respect to R^5 except a hydrogen atom, halogen atoms and groups which are directly bonded to the quinazoline skeleton through a carbon atom;

$R^6{}_b$ is a group selected from among those defined above with respect to R^6 except halogen atoms; and

F represents an eliminable group).

That is, this process is one for preparing an objective compound (VIII) by condensing a compound represented by the general formula (VII) with a compound represented by the general formula (IX).

The eliminable group represented by F in the formula includes, for example, halogen atoms, alkylthio groups and so forth.

This process may be conducted in the presence of a base at need.

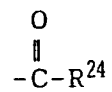
The base includes organic bases such as triethylamine, pyridine and diisopropylethylamine; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium hydroxide and sodium hydride; and alkoxides such as sodium methoxide and potassium t-butoxide.

As the reaction solvent, every solvent which is inert to the reaction can be used and examples thereof include ethanol, isopropanol, tetrahydrofuran, dimethylformamide and dimethyl sulfoxide.

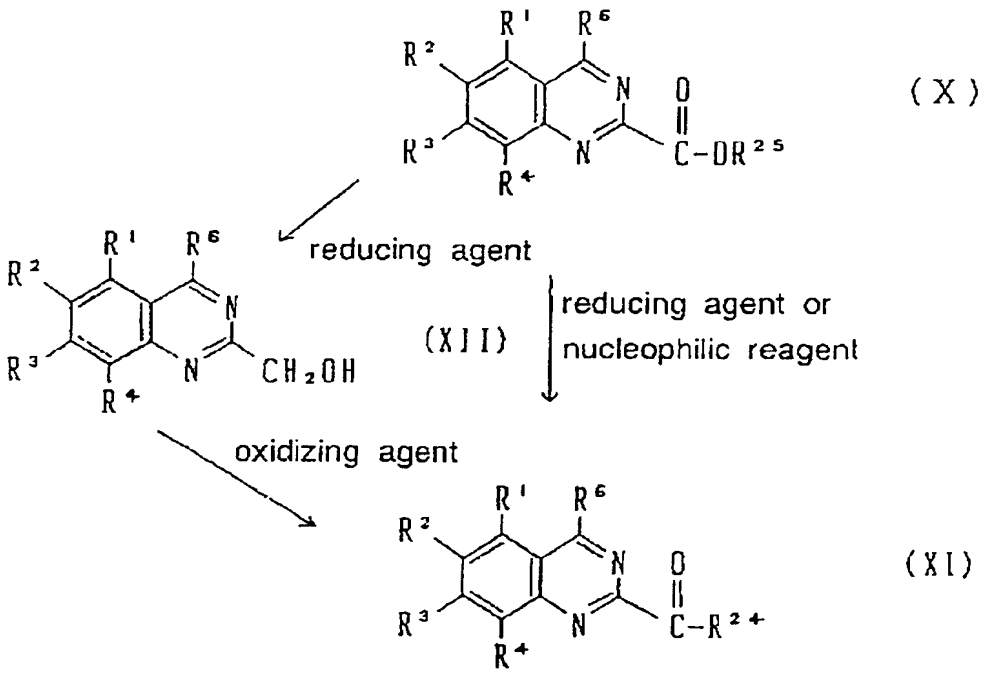
The reaction temperature preferably ranges from 0 to 300 °C.

Preparation process 4

When R^5 is a group represented by the formula



(wherein R^{24} is a hydrogen atom or a lower alkyl group in the general formula (I), a compound represented by the general formula (I) can also be prepared by the following process:



(in a series of formulas, R^1, R^2, R^3, R^4 and R^6 are each as defined above; and R^{24} and R^{25}, each of which may be the same or different from each other, represent each a hydrogen atom or a lower alkyl group).

That is, this process is one for preparing an objective compound (XI) by reacting a compound represented by the general formula (X) with an ordinary reducing agent or an ordinary nucleophilic reagent, either directly or through the oxidation of an alcohol (XII).

The reducing agent includes lithium aluminum hydride, sodium borohydride, diisobutylaluminum hydride and so forth.

The nucleophilic reagent includes lower alkyl metals such as methyllithium, methylmagnesium bromide and so forth.

The oxidizing agent to be used when the reaction is conducted through the alcohol (XII) includes potassium bichromate/sulfuric acid, dimethyl sulfoxide/oxalyl chloride and so forth.

As the reaction solvent, every solvent which is inert to the reaction can be used.

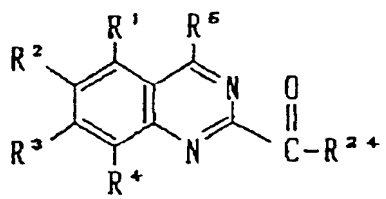
The reaction temperature ranges from 0 °C to the refluxing temperature of the solvent.

Preparation process 5

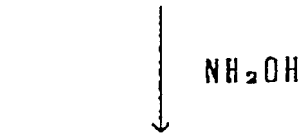
When R^5 is a group represented by the formula

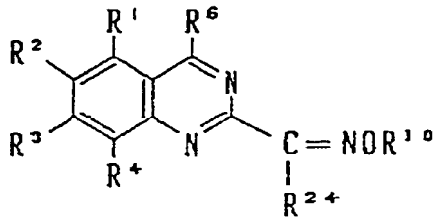
$$-C(=N-OR^{10})-R^{24}$$

(wherein R^{10} and R^{24} are each as defined above) in the general formula (I), a compound represented by the general formula (I) can also be prepared by the following process:



(XI)





(XIII)

(in a series of formulas, R^1, R^2, R^3, R^4, R^6, R^{10} and R^{24} are each as defined above).

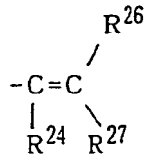
That is, this process is one for preparing a compound represented by the formula (XIII) by reacting a compound represented by the general formula (XI) with hydroxyamine.

As the reaction solvent, every solvent which is inert to the reaction can be used.

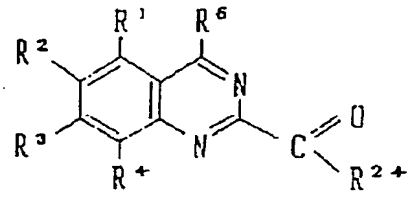
The reaction temperature ranges form 0 °C to the refluxing temperature of the solvent.

Preparation process 6

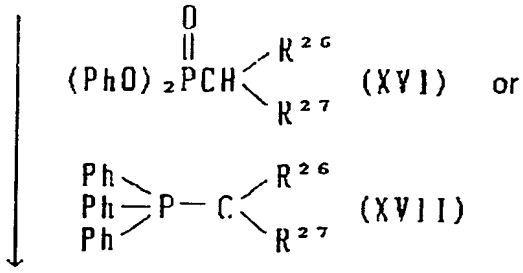
When R^5 is a group represented by the formula



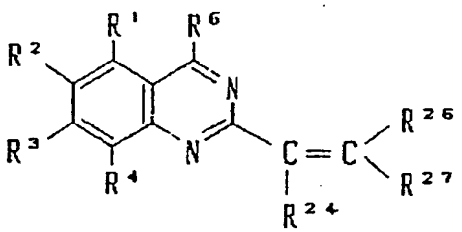
(wherein R^{24} is as defined above; R^{26} represents a hydrogen atom or a lower alkyl group; and R^{27} represents a hydrogen atom, a lower alkyl group, a carboxyl group which may be protected or a carboxyalkyl group which may be protected) in the general formula (I), a compound represented by the formula (I) can also be prepared by the following process:



(XIV)



(XVI) or (XVII)



(XV)

(in a series of formulas, R^1, R^2, R^3, R^4, R^6, R^{24}, R^{26} and R^{27} are each as defined above; and Ph represents a phenyl group).

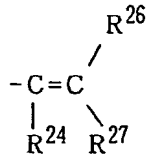
That is, this process is one for preparing a compound represented by the general formula (XV) by reacting a compound represented by the general formula (XIV) with a compound represented by the general formula (XVI) or the general formula (XVII) through the Wittig reaction.

As the reaction solvent, every solvent which is inert to the reaction can be used.

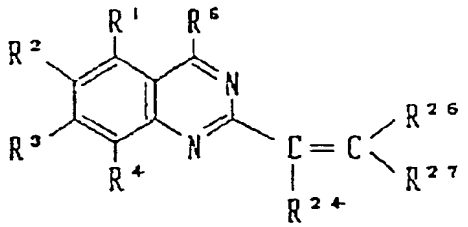
The reaction temperature ranges from 0 °C to the refluxing temperature of the solvent.

Preparation process 7

When R^5 is a group represented by the formula

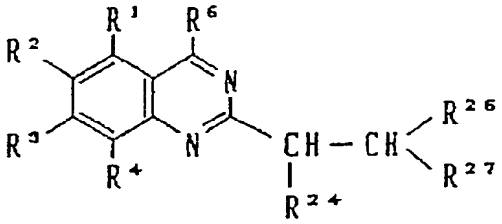


(wherein R^{24}, R^{26} and R^{27} are each as defined above) in the general formula (I), a compound represented by the formula (I) can also be prepared by the following process:



(XV)

Pd-C or Pt



(XVIII)

(in a series of formulas, R^1, R^2, R^3, R^4, R^6, R^{24}, R^{26} and R^{27} are each as defined above).

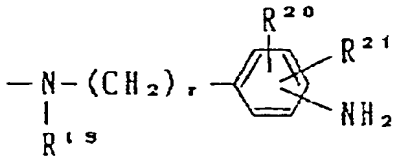
That is, this process is one for preparing an objective compound (XVIII) by reducing the compound represented by the general formula (XV) prepared in the Preparation process 6.

The reduction can be conducted by conventional means, for example, catalytic reduction using palladium/carbon or platinum catalyst.

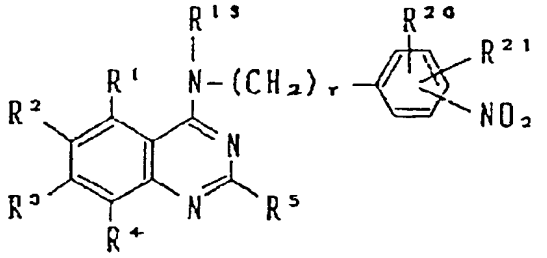
As the reaction solvent, every solvent which is inert to the reaction is used.

Preparation process 8

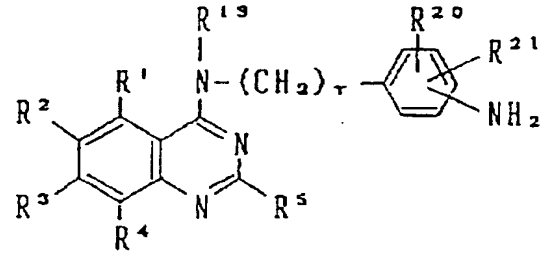
When R^6 is a group represented by the formula



(wherein R^{19}, R^{20}, R^{21} and r are each as defined above) in the general formula (I), a compound represented by the general formula (I) can also be prepared by the following process:



(XIX)



(XX)

(in a series of formulas, R^1, R^2, R^3, R^4, R^5, R^{19}, R^{20}, R^{21} and r are each as defined above).

That is, this process is one for preparing an objective compound (XX) by reducing a compound represented by the general formula (XIX).

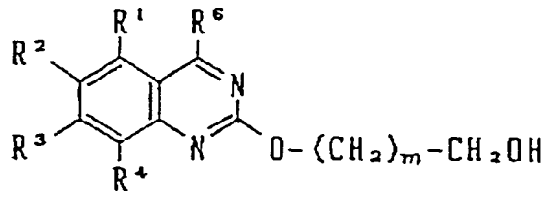
The reduction is conducted by conventional means. e.g., catalytic reduction using palladium/carbon or platinum catalyst or reduction with iron or tin.

As the reaction solvent, every solvent which is inert to the reaction can be used.

Preparation process 9

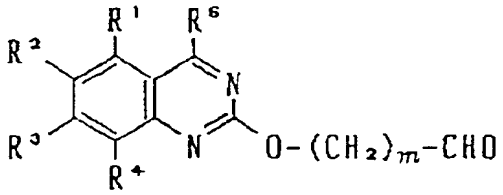
When R^5 is a group represented by the formula -O-$R^{9'}$ (wherein $R^{9'}$ is a carboxyl group which may be protected) in the general formula (I), a compound represented by the formula (I) can be prepared by the following process:

(The first step)



(XXI)

Oxidation



(XXII)

(in a series of formulas, R^1, R^2, R^3, R^4 and R^6 are each as defined above; and m represents 0 or an integer of 1 to 2).

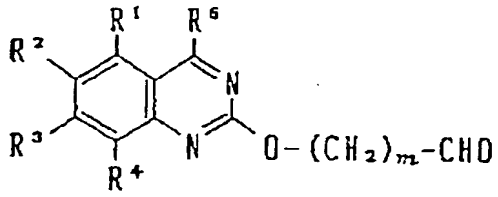
That is, this process is one for preparing a compound represented by the general formula (XXII) by oxidizing a compound represented by the general formula (XXI) by conventional means.

As the oxidizing agent, everyone can be used so far as it is conventionally used and examples thereof include chrominum (VI), dimethyl sulfoxide and oxalyl chloride.

As the reaction solvent, every solvent which is inert to the reaction can be used.

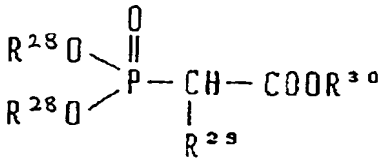
The reaction temperature ranges from 0 °C to the refluxing temperature of the solvent.

(The second step)



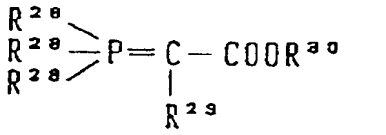
(XXII)

+

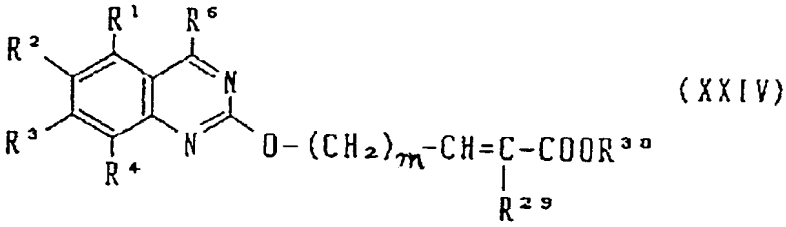


(XXIII)

or



(XXIII)'



(XXIV)

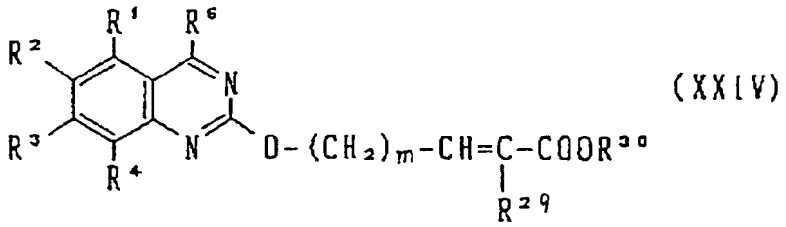
(in a series of formulas, R^1, R^2, R^3, R^4, R^6 and m are each as defined above; and R^{28}, R^{29} and R^{30}, each of which may be the same or different from one another, represent each a hydrogen atom or a lower alkyl group).

That is, this process is one for preparing a compound represented by the general formula (XXIV) by reacting the compound (XXII) prepared in the first step with the Wittig reagents (XXIII) or (XXIII)'.

As the reaction solvent, everyone which is inert to the reaction can be used.

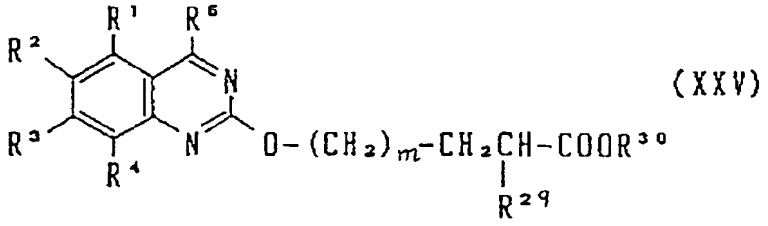
The reaction temperature ranges from 0 °C to the refluxing temperature of the solvent.

(The third step)



(XXIV)

reduction



(XXV)

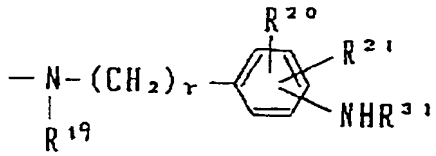
(in a series of formulas, R^1, R^2, R^3, R^4, R^6, R^{29}, R^{30} and m are each as defined above).

That is, this process is one for preparing the objective compound (XXV) by reducing the compound (XXIV) prepared in the second step.

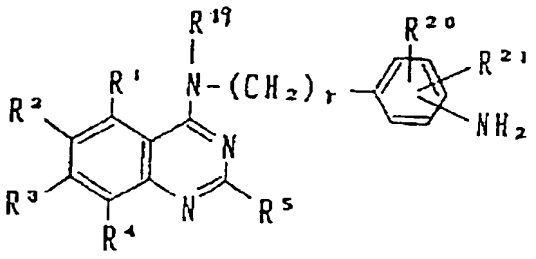
The reduction may be conducted by conventional means, and examples thereof include catalytic reduction using palladium/carbon or platinum catalyst.

Preparation process 10

When R^6 is a group represented by the formula



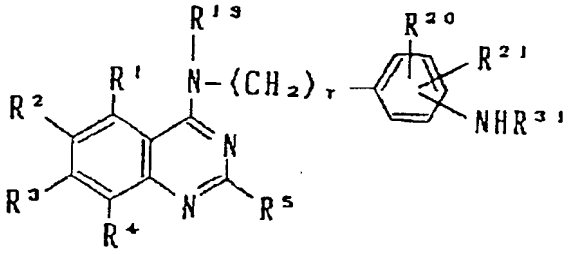
(wherein R^{19}, R^{20}, R^{21} and r are each as defined above; and R^{31} represents an acyl group, a lower alkylsulfonyl group or a lower alkyloxycarbonyl group) in the general formula (I), a compound represented by the general formula (I) can also be prepared by the following process:



(XX)

acylation or
sulfonylation or
alkoxycarbonylation

base



(XXVI)

(in a series of formulas, R^1, R^2, R^3, R^4, R^5, R^{19}, R^{20}, R^{21}, R^{31} and r are each as defined above).

That is, this process is one for preparing an objective compound (XXVI) by subjecting the compound represented by the general formula (XX) prepared in the Preparative process 8 to the conventional acylation, sulfonylation or alkoxycarbonylation in the presence of a base.

As the acylating agent, every acylating agent which is conventionally used, for example, activated derivatives of carboxylic acids such as acid chloride, acid anhydride and mixed acid anhydride; and condensing agents such as dicyclohexylcarbodiimide is used.

As the sulfonylating agent, every sulfonylating agent which is conventionally used can be used and examples thereof include a lower alkylsulfonyl chloride and a lower alkylsulfonic anhydride.

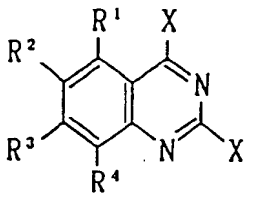
The alkoxycarbonylating agent includes every alkoxycarbonylating agent which is conventionally used, for example, a lower alkyloxycarbonyl chloride and a lower alkyl pyrocarbonate.

As the base, every base can be used and examples thereof include organic bases such as pyridine and triethylamine; and inorganic bases such as sodium carbonate, potassium carbonate, sodium hydroxide and sodium hydride.

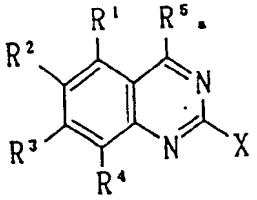
Preparation process 11

When the ring A is selected from any of a benzene ring, a pyridine ring and a cyclohexane ring, the ring B is selected from among a pyridine ring, a pyrimidine ring and an imidazole ring, R^5 represents a group selected from among those defined above with respect to R^5 except groups which are directly bonded to the ring portion through a carbon atom; and R^6 represents a group selected from among those defined above with respect to R^5 except groups which are directly bonded to the ring portion through a carbon atom in the general formula (1), the compound represented by the general formula (1) can also be prepared by the following process. The case in which the ring portion forms a quinazoline skeleton is shown below as the representative of the above:

(The first step)



(XXVII)



(XXVIII)

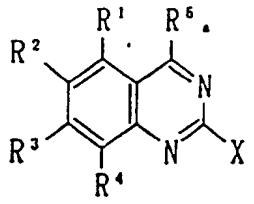
(in a series of formulas, R^1, R^2, R^3 and R^4 are each as defined above; $R^5{}_a$ represents a group selected from among those defined above with respect to R^5 except groups which are directly bonded to the ring portion through a carbon atom; and X represents a halogen atom).

That is, the first step is a condensation reaction according to a conventional process.

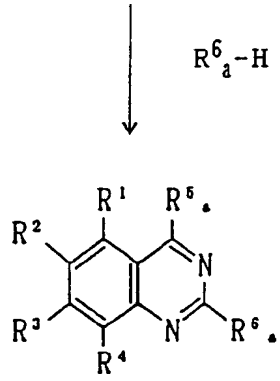
Alcohol solvents such as isopropyl alcohol, ether solvents such as tetrahydrofuran and dimethylformamide are preferably used as the reaction solvent. However, every solvent which is inert to the reaction can be used.

In the case where $R^5{}_a$ is bonded to the ring portion through a nitrogen atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of a tertiary amine such as triethylamine while removing HCl generated. While in the case where $R^5{}_a$ is bonded to the ring portion through an oxygen atom or a sulfur atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of an alkali such as sodium hydroxide and sodium carbonate.

(The second step)



(XXVIII)



(XXIX)

(in a series of formulas, R^1, R^2, R^3, R^4, $R^5{}_a$ and X are each as defined above; $R^6{}_a$ represents a group selected from among those defined above with respect to R^6 except groups which are directly bonded to the ring portion through a carbon atom).

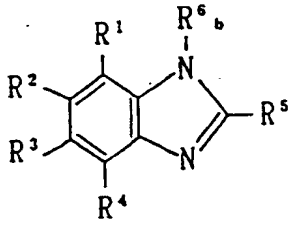
The second step is a reaction wherein the compound (XXVIII) obtained in the first step is condensed with a compound represented by the formula $R^6{}_a$-H according to a conventional process.

Alcohol solvents such as isopropyl alcohol, ether solvents such as tetrahydrofuran and dimethylformamide are preferably used as the reaction solvent. However, every solvent which is inert to the reaction can be used.

In the case where $R^6{}_a$ is bonded to the ring portion through a nitrogen atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of an organic base such as triethylamine, pyridine and ethyldiisopropylamine, an inorganic base such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium hydride and sodium hydroxide or an alkoxide such as sodium methoxide and potassium t-butoxide. While in the case where $R^6{}_a$ is bonded to the ring portion through an oxygen atom or a sulfur atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of an alkali such as sodium hydroxide and sodium carbonate.

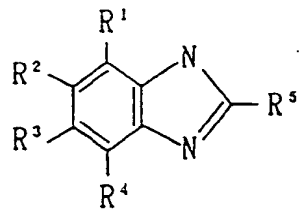
Preparation process 12

When the compound represented by the general formula (1) is a compound represented by the following general formula (XXXII):



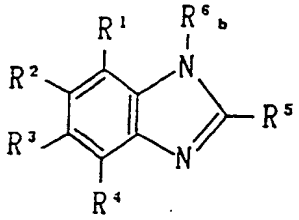
(XXXII)

the compound can also be prepared by the following process.



(XXX)

$R^6{}_b$-Cl (XXXI)/NaI



(XXXII)

(in a series of formulas, R^1, R^2, R^3, R^4 and R^5 are each as defined above; and $R^6{}_b$ represents a group selected from among groups which are directly bonded to the ring portion through a carbon atom in those defined above with respect to R^6).

That is, this process is one for preparing an objective compound by reacting, for example, piperonyl chloride (XXXI) with a benzimidazole derivative represented by the general formula (XXX) in the presence of an alkali by a conventional process.

Sodium iodide is preferred as alkali.

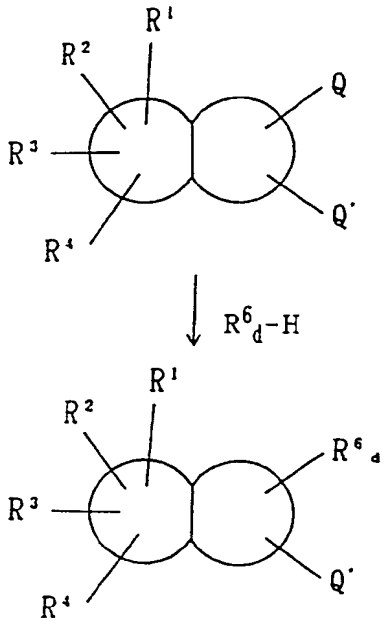
Although every solvent which is inert to the reaction can be used as the reaction solvent, polar solvents such as dimethylforamide can be cited as preferable ones.

The reaction temperature is preferably about 60 to 100 °C, particularly preferably about 70 to 80 °C.

Preparation process 13

The compound of the present invention can also be prepared by the following process:

(The first step)



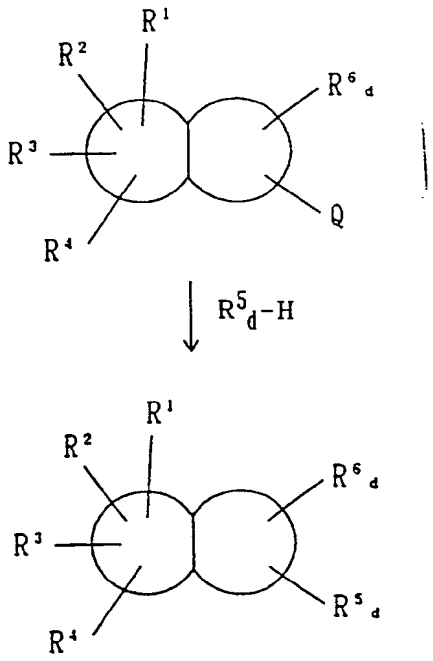
(in a series of formulas, R^1, R^2, R^3 and R^4 are each as defined above; $R^6{}_d$ represents a group selected from among those defined above with respect to R^6 except groups which are directly bonded to the ring portion through a carbon atom; and Q and Q' represent halogen atoms).

The first step is a condensation reaction according to a conventional process.

In the case where $R^6{}_d$ is bonded to the ring portion through a nitrogen atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of an organic base such as triethylamine, pyridine and diisopropylethylamine, an inorganic base such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium hydroxide and sodium hydride or an alkoxide such as sodium methoxide and potassium t-butoxide. While in the case where $R^6{}_d$ is bonded to the ring portion through an oxygen atom or a sulfur atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of an inorganic base such as sodium hydroxide and sodium carbonate.

Every solvent which is inert to the reaction can be used as the reaction solvent, and examples thereof include alcohol solvents such as ethanol and isopropyl alcohol, ether solvents such as tetrahydrofuran, dimethylformamide and dimethylsulfoxide. Further, in the present process, the reaction can be proceeded in the absence of a reaction solvent in some cases.

(The second step)



(in a series of formulas, R^1, R^2, R^3, R^4, $R^5{}_d$ and Q are each as defined above; and $R^5{}_d$ represents a group selected from among those defined above with respect to R^5 except groups which are directly bonded to the ring portion through a carbon atom).

That is, the second step is a process for preparing an objective compound in which the compound obtained in the first step is condensed with a compound represented by the general formula $R^5{}_d$-H.

In the present process, the reaction can be proceeded in the presence of a base at neeed.

As the base, organic bases such as triethylamine, pyridine and diisopropylethylamine, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium hydroxide and sodium hydride and alkoxides such as sodium methoxide and potassium t-butoxide can be cited.

Every solvent which inert to the reaction can be used as the reaction solvent, and examples thereof include alcohol solvents such as ethanol and isopropanol, ether solvents such as tetrahydrofuran, dimethylformamide and dimethylsulfoxide.

The reaction temperature is preferably 0 °C to 300 °C.

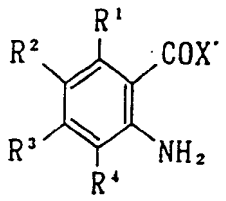
In the case where $R^5{}_d$ is a group which is bonded to the ring portion through a nitrogen atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of a tertiary amine such as triethylamine. While in the case where $R^5{}_d$ is a group which is bonded to the ring portion through an oxygen atom or a sulfur atom, it is preferred that the reaction is proceeded by heating under reflux in the presence of an alkali such as sodium hydroxide and sodium carbonate.

The compounds thus obtained in the preparation processes 1 to 13 described above can form salts thereof by a conventional process, for example, by adding sodium hydroxide, potassium hydroxide or methanesulfonic chloride.

Next, the preparation processes for the raw compounds used in the preparation processes will be shown.

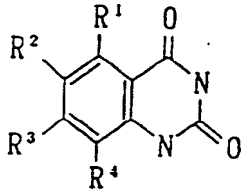
Preparation process A

Among the starting materials used in the preparation process 13, the compound in which the ring portion is a quinazoline ring and Q and Q' are chlorine atoms can also be prepared by the following process:



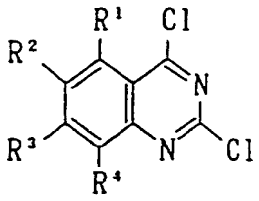
(a)

(the first step)



(b)

(the second step)



(c)

(in a series of formulas, R^1, R^2, R^3 and R^4 are each as defined above; and X' represents any group among a hydroxyl group, an alkoxy group and an amino group).

That is, this process is one for preparing the objective compound (c) by cyclizing the compound (a) by a conventional process to obtain the compound (b) and then chlorinating it by a conventional process.

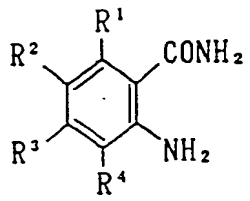
The first step is a cyclization reaction. It is a step in which urea is reacted with the compound (a) to obtain the compound (b). In this case, the reaction temperature is preferably about 170 to 190 °C, and although every solvent can be used as long as it is inert to the reaction, preferable examples thereof include N-methylpyrrolidone and the like. In this step, the reaction can also be proceeded in the absence of the solvent.

Further, the compound (b) can also be obtained by cyclizing with carbonyldiimidazole or by cyclizing under an acidic or basic condition after converting to urethane with a chloroformic ester when X' is an amino group.

The second step is a chlorination reaction. This step can be carried out by a conventional manner, and examples thereof include a process in which the compound (b) is heated under reflux with phosphorus pentachloride and phosphorus oxychloride, or phosphorus oxychloride while stirring to chlorinate.

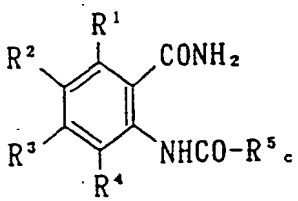
Preparation process B

The starting material (II) used in the preparation process 1 can be prepared by the following process:



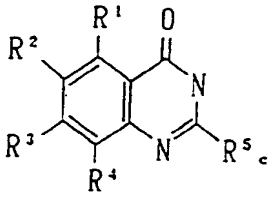
(d)

(the first step) acylating agent such as acid chloride/base



(e)

(the second step) acid or base



(f)

(in a series of formulas, R^1, R^2, R^3 and R^4 are each as defined above; and $R^5{}_c$ represents a halogen atom or a group selected from among groups which are directly bonded to the ring portion through a carbon atom in those defined with respect to above R^5).

That is, the above process is a reaction in which an amide product is obtained by a conventional process in the first step and a cyclization is carried out in the presence of an acid or a base in the second step.

The amide product (e) can be obtained by a conventional process, and it can be obtained, for example, by reacting the compound (d) with an acylating agent such as an acid chloride represented by $R^5{}_c$-COCl in the presence of a base.

Tertiary amines such as triethylamine and organic bases such as pyridine are preferably cited as the base.

Specific examples of the acylating agent include acid chlorides such as benzoyl chloride, acetyl chloride, ethyloxalyl chloride and benzyloxyacetyl chloride.

The reaction temperature is preferably about 0 °C to 30 °C.

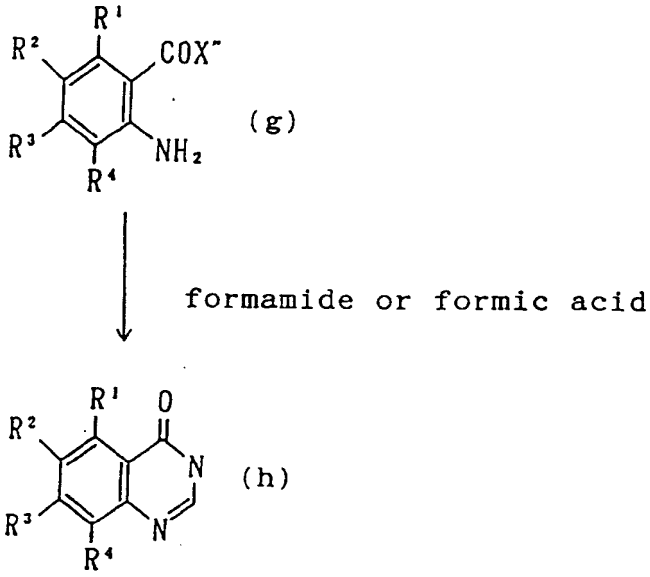
In the second step, the compound (e) obtained in the first step is heated under reflux in the presence of an acid or a base to obtain the compound (f).

The acid includes acetic anhydride and the like.

The base includes sodium hydroxide and the like.

Preparation process C

The starting material (II) can also be prepared by the following process when $R^5{}_a$ is a hydrogen atom in the preparation process 1:



(in a series of formulas, R^1, R^2, R^3 and R^4 are each as defined above; and X" represents a hydroxyl group or a lower alkoxy group).

That is, the above process is a cyclization reaction by a conventional process.

The objective compound (h) can be synthesized, for example, by condensing the raw compound (g) with formamide by heating under reflux, or by heating it together with formic acid.

[Effect of the Invention]

Experimental Examples will now be described to illustrate the effect of the compound of the present invention.

Experimental Examples

Enzyme inhibiting action with the use of cGMP-PDE prepared from the swine aeorta

1. Method of experiment

The enzymatic activity of the cGMP-PDE prepared from the swine aeorta was determined according to the method of Thompson et al.(1). The enzymatic activity thereof was determined in the presence of 1 mM EGTA by the use of 1 μM cGMP as a substrate. The compound of the present invention was dissolved in DMSO, added to the reaction liquid and examined for the inhibitory activity. The final concentration of DMSO in the reaction liquid was adjusted to 4% or below.

Preparation of cGMP-PDE

The swine aeorta was sliced, followed by the addition of 10 times by volume as much Buffer A (20mM Tris/HCl, 2mM Mg acetate, 1mM Dithiothreitol, 5mM EDTA, 1400TIU/liter aprotinin, 10 mg/liter leupeptin, 1mM benzamidine, 0.2mM PMSF, pH 7.5). The obtained mixture was homogenized and the homogenate

(1) Thompson, W.J. and Strada, S. J., Cyclic Nucleotide Phosphodiesterase (PDE), in Methods of Enzymatic Analysis, vol 4, p.127-234, 1984.

was centrifuged at 100000 × g for one hour. The obtained supernatant was supplied a DEAE-Toyopearl 650S (Tosoh, Tokyo, Japan) column. After the column was washed with Buffer B (50mM Tris/HCl, 0.1mM EGTA, 2mM Mg acetate, 1mM Dithiothreitol, 0.2mM PMSF, pH 7.5), gradient elution with 0.05 to 0.4 M NaCl was conducted. Thus, CaM-independent cGMP-PDE fractions were obtained.

2. Results of experiment

The results of experiment of the compounds of the present invention are given in Tables 1 to 6B.

Table 1

Ex. No.	IC_{50} (μM)
7	1.0
19	0.39
22	0.36
25	0.78
33	0.37
38	0.42
40	0.65
41	0.35
42	0.19
45	0.41
46	0.24
49	0.041
50	0.032
51	0.069
52	0.069
53	0.12
54	0.47
55	0.030
57	0.038
58	0.042
59	0.27
60	0.18
61	0.42

Table 2

Ex. No.	$IC_{50}(\mu M)$
64	0.38
65	0.093
67	0.14
68	0.62
69	0.19
70	0.84
71	0.81
72	0.73
73	0.94
74	0.35
78	0.50
81	0.44
82	0.55
83	0.024
84	0.22
86	0.96
87	0.68
89	0.16
91	0.036
92	0.094
93	0.032
95	0.20
97	0.79

Table 3

Ex. No.	IC_{50} (μM)
98	0.062
104	0.010
105	0.18
107	0.0040
114	0.0030
112	0.0020
115	0.0020
120	0.0010
121	0.65
122	0.0050
123	0.031
124	0.0080
125	0.0090
126	0.0010
127	0.11
128	0.30
133	0.77
134	0.0050
136	0.93
137	0.38
138	0.81
139	0.021
140	0.68

Table 4

Ex. No.	$IC_{50}(\mu M)$
146	0.015
150	0.0072
151	0.081
152	0.11
164	0.0080
165	0.016
166	0.026
167	0.56
168	0.011
169	0.011
170	0.029
171	0.00040
172	0.095
174	0.0040
175	0.0060
176	0.0030
177	0.012
178	0.011
179	0.0020
180	0.0090
181	0.0050
182	0.0080
183	0.00040

Table 5

Ex. No.	$IC_{50}(\mu M)$
184	0.0060
185	0.010
187	0.12
188	0.029
189	0.016
190	0.0050
191	0.019
192	0.020
193	0.00080
194	0.0040
197	0.066
200	0.064
201	0.049
202	0.0020
203	0.028
204	0.0040
206	0.029
208	0.00019
213	0.023
214	0.0090
216	0.017
220	0.00024
222	0.0065

Table 6A

Ex. No.	IC_{50}(μM
227	0.0026
228	0.00052
230	0.0058
231	0.41
232	0.044
233	0.013
234	0.0060
235	0.0020
236	0.0060
237	0.014
238	0.0050
239	0.0080
240	0.0040
241	0.18
243	0.00015
244	0.0090
245	0.10

Table 6B

Ex. No.	IC_{50}(μM
255	0.032
256	0.0021
260	0.00016
262	0.88
266	0.11
278	0.25
280	0.25
376	0.021

It became apparent from the above experimental examples that the compounds of the present invention exhibit PDE, particularly cGMP-PDE, inhibiting action. That is, it became obvious that the compounds of the present invention exhibit the effect to increase the concentration of cGMP in vivo by revealing the cGMP-PDE inhibiting action. Accordingly, the nitrogenous heterocyclic compounds which are the compounds of the present invention are effective in the prevention and medical treatment of diseases for which cGMP-PDE inhibiting action is efficacious. Examples of these diseases include ischemic heart disease such as angina pectoris, myocardial infarction and chronic and acute cardiac failures, lung hypertension which may accompany with cor pulmonale, other hypertensions attributable to all causes, peripheral circulatory disturbance, brain circulatory diturbance, brain function diturbance and allergic diseases such as bronchial asthma, atopic dermatitis and allergic rhinitis.

Those inhibiting a calmodulin-depending type PDE are also included in the compound group of the present invention. There is high possibility that the diseases for which this action is efficacious are the same as the diseases for which cGMP-PDE inhibitoy action described above is efficacious, and, also from this point, it can be said that the compounds of the present invention can be used for prevention and medical treatment of the diseases described above.

Further, the compounds of the present invention are lowly toxic and therefore are extremely safe. Therefore, the present invention is valuable also from this standpoint.

When the compounds of the present invention are used as drugs for these diseases, they may be each administered orally or parenterally. The dose varies depending upon the extent of symptom; age, sex, weight and sensitivity of a patient; the method of administration; the timing and interval of administration, the properties, dispensing and kind of medical preparation; and the kind of an active ingredient and is not particularly limited.

In orally administration, the dose thereof per adult a day is generally about 1 to 1000 mg, preferably about 5 to 500 mg, still preferably 10 to 100 mg, which may be generally administered in 1 to 3 portions a day.

In the case of an injection, the dose thereof is generally 1 μg/kg to 3,000 μg/kg, preferably about 3 μg/kg to 1,000 μg/kg.

In the preparation of a solid preparation for oral administration, a filler and, if necessary, a binder, disintegrator, lubricant, color and/or corrigent is(are) added to the active ingredient and then there is shaped into a tablet, a coated tablet, granule, powder or a capsule by a conventional manner.

Examples of the filler to be used include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide; those of the binder to be used include polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylmethylcellulose, calcium citrate, dextrin and pectin; those of the lubricant to be used include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oil; those of the color to be used include those authorized as pharmaceutical additives; and those of the corrigent to be used include cocoa powder, mentha herb, aromatic acid, mentha oil, borneol and powdered cinnamon bark. Of course, the tablet and granule may be suitably coated with sugar, gelatin or the like, if necessary.

In the preparation of an injection, a pH modifier, buffer, suspending agent, solubilizing agent, stabilizer, tonicity agent and/or preservative is(are) added to the active ingredient at need and then there is formulated into an injection for intravenous, subcutaneous or intramuscular administration by a conventional manner. It is also necessary that the injection is freeze-dried according to a conventional method.

Examples of the suspending agent include methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, tragacanth powder, sodium carboxymethylcellulose and polyoxyethylene sorbitan monolaurate.

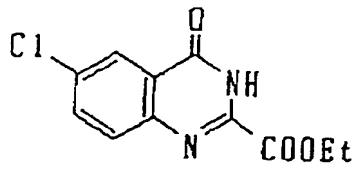
Examples of the solubilizing agent include polyoxyethylene hardened castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol and ethyl ester of castor oil fatty acid.

[Example]

Examples of the present invention will now be described, though it is needless to say that the present invention is not limited to them. In advance of Examples, preparative example of the raw compound for compounds according to the present invention will be described. In the Examples, Me represents a methyl group, Et an ethyl group, Bzl a benzyl group and Ac an acetyl group.

Preparative Example 1

2-Ethoxycarbonyl-6-chloroquinazolin-4(3H)-one



2.50 g (0.0147 mol) of 2-amino-5-chlorobenzamide was dissolved in 15 ml of pyridine. 2.0 ml of ethyloxalyl chloride was dropped into the obtained solution under stirring at room temperature. The obtained mixture was stirred for several hours and distilled under a reduced pressure to remove the solvent. The obtained residue was used as such in the subsequent reaction.

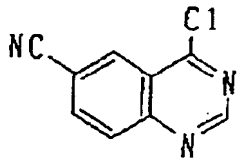
The residue was dissolved in 50 ml of acetic acid, followed by the addition of 5 ml of acetic anhydride. The obtained mixture was heated under reflux for 24 hours. The solvent was distilled away under a reduced pressure and ethanol was added to the obtained crystalline residue. The obtained mixture was filtered to recover the crystal. The crystal was washed with ethanol and ether and air-dried to give 2.78 g of the title compound as a pale-yellow crystal.

- yield(%); 75
- m.p.(°C); 239 ~ 240
- Mass; 253 $(M+H)^+$
- NMR δ (DMSO-d_6);

  1.36 (3H, t, J=7.2Hz), 4.39 (2H, q, J=7.2Hz), 7.86 (1H, d, J=8.8Hz), 7.92 (1H, dd, J=8.8Hz, 2.4Hz), 8.11 (1H, d, J=2.4Hz), 12.85 (1H, brs)

Example 1

4-Chloro-6-cyanoquinazoline



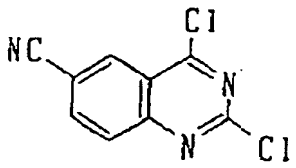
A mixture comprising 2 g of 4-hydroxy-6-carbamoylquinazoline, 30 ml of thionyl chloride and 60 ml of phosphorus oxychloride was heated under reflux for 20 hours. The reaction mixture was concentrated under a reduced pressure and the obtained residue was dissolved in 100 ml of ethyl acetate. The obtained solution was washed with water (150 ml), dried over magnesium sulfate and concentrated under a reduced pressure. The obtained residue was introduced into a silica gel column, followed by eluting with ethyl acetate and acetone to give 800 mg of the title compound.

- molecular formula; $C_3H_4N_3Cl$ (189.5)
- yield(%); 40
- m.p.(°C); >290
- Mass; 190 $(M+1)^+$
- NMR δ (DMSO-d_6);

  7.79 (1H, d, J=8.8Hz), 8.16 (1H, dd, J=8.8Hz, 2.0Hz), 8.26 (1H, s), 8.49 (1H, d, J=2.0Hz)

Example 2

2,4-Dichloro-6-cyanoquinazoline

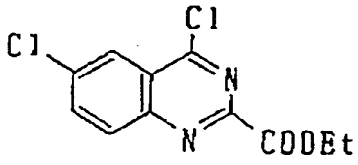


12 g of 2,4-dihydroxy-6-carbamoylquinazoline and 48.8 g of phosphorus pentachloride were suspended in a mixture comprising 200 ml of phosphorus oxychloride and 70 ml of thionyl chloride and the obtained suspension was heated under reflux for 24 hours. The reaction mixture was concentrated under a reduced pressure and the obtained crystalline residue was washed with 100 ml of ethyl acetate and 100 ml of n-hexane to give 6.8 g of the title compound.

- molecular formula; $C_3H_3Cl_2N_3$
- yield(%); 52
- m.p.(°C); 161 ~ 163
- Mass; 224 $(M+1)^+$
- NMR δ ($CDCl_3$);
  7.94 (1H, d, J=8.0Hz), 8.00 (1H, dd, J=8.0Hz, 2.0Hz), 8.49 ((1H, d, J=2.0Hz)

Example 3

2-Ethoxycarbonyl-4,6-dichloroquinazoline

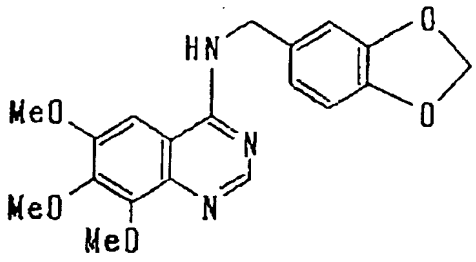


2.68 g (0.0106 mol) of 2-ethoxycarbonyl-6-chloroquinazolin-4(3H)-one obtained in Preparative Example 1 was suspended in 40 ml of phosphorus oxychloride. The suspension was heated under reflux for one hour and distilled under a reduced pressure to remove the solvent. The residue was dissolved in ethyl acetate and the obtained solution was washed with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was recovered, dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to remove the solvent, giving 2.82 g of the title compound as a pale-yellow crystal.

- yield(%); 98
- m.p.(°C); 129 ~ 130
- Mass; 271 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.50 (3H, t, J=7.2Hz), 4.60 (2H, q, J=7.2Hz), 7.99 (1H, dd, J=8.8Hz, 2.4Hz), 8.25 (1H, d, J=8.8Hz), 8,34 (1H, d, J=2.4Hz)

Example 4

4-(3,4-Methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



21.2 g (0.083 mol) of 4-chloro-6,7,8-trimethoxyquinazoline, 17.0 g (0.112 mol) of piperonylamine and 13.5 g (0.127 mol) of sodium carbonate were mixed with 400 ml of isopropyl alcohol. The obtained mixture was heated under reflux for 24 hours and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate) and recrystallized from ethyl acetate to give 21.3 g of the title compound as a pale-yellow needle.

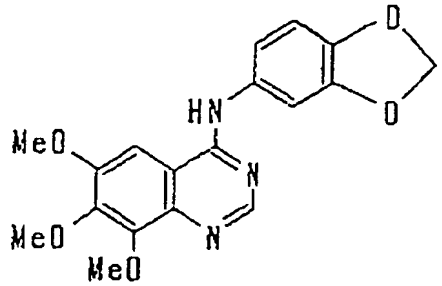
- molecular formula; $C_{19}H_{19}N_3O_5$
- yield(%); 69
- m.p.(°C); 197 ~ 198
- Mass; 370 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.94 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.76 (2H, d, J=8.0Hz), 5.55 (1H, brs), 5.97 (2H, s), 6.64 (1H, s), 6.80 (1H, d, J=8.0Hz), 6.87 (1H, d, J=8.0Hz), 6.91 (1H, s), 8.66 (1H, s)

Examples 5 to 48

The following compounds were prepared in a similar manner to that of Example 4.

Example 5

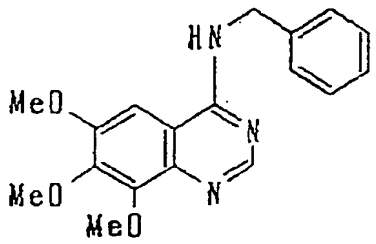
4-(3,4-Methylenedioxyphenyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_5$
- yield(%); 58
- m.p.(°C); 254 ~ 255 (dec.)
- Mass; 356 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.02 (3H, s), 4.05 (3H, s), 4.13 (3H, s), 5.99 (2H, s), 6.83 (1H, d, J=7.6Hz), 7.02 (1H, d, J=7.6Hz), 7.32 (1H, s), 7.33 (1H, s), 8.49 (1H, brs), 8.63 (1H, s)

Example 6

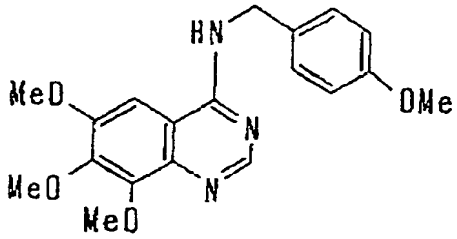
4-Benzylamino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{19}N_3O_3$
- yield(%); 91
- m.p.(°C); 180 ~ 181
- Mass; 326 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.94 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.87 (2H, d, J=5.2Hz), 5.62 (1H, brs), 6.65 (1H, s), 7.4 (5H, m), 8.67 (1H, s)

Example 7

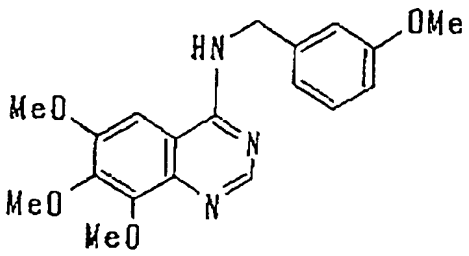
4-(4-Methoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{21}N_3O_4$
- yield(%); 97
- m.p.(°C); 174 ~ 175
- Mass; 356 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.82 (3H, s), 3.93 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.79 (2H, d, J=4.8Hz), 5.53 (1H, brs), 6.63 (1H, s), 6.92 (2H, d, J=8.4Hz), 7.35 (2H, d, J=8.4Hz), 8.67 (1H, s)

Example 8

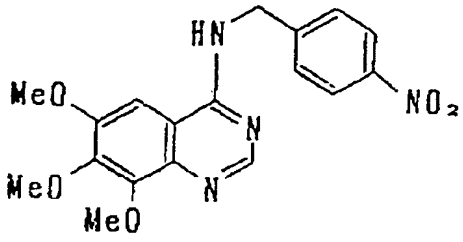
4-(3-Methoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{21}N_3O_4$
- yield(%); 89
- m.p.(°C); 142 ~ 143
- Mass; 356 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.80 (3H, s), 3.96 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.85 (2H, d, J=4.8Hz), 5.96 (1H, brs), 6.76 (1H, s) 6.86 (1H, d, J=8.0Hz), 6.99 (1H, d, J=8.0Hz), 7.02 (1H, s), 7.29 (1H, t J=8.0Hz), 8.65 (1H, s)

Example 9

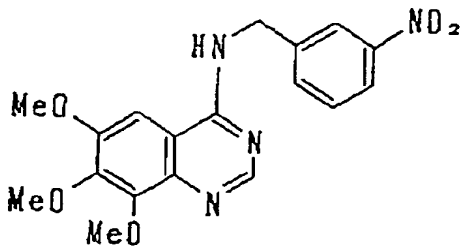
4-(4-Nitrobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{18}N_4O_5$
- yield(%); 28
- m.p.(°C); 210 ~ 212
- Mass; 371 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.05 (3H, s), 4.13 (3H, s), 5.01 (2H, d, J=5.6Hz), 5.96 (1H, brs), 6.76 (1H, s), 7.54 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.8Hz), 8.62 (1H, s)

Example 10

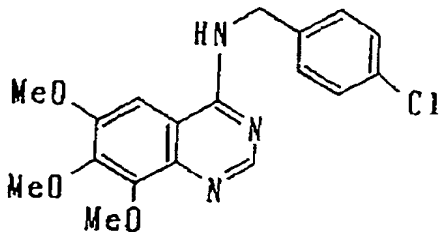
4-(3-Nitrobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{18}N_4O_5$
- yield(%); 30
- m.p.(°C); 159 ~ 160
- Mass; 371 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.04 (3H, s), 4.12 (3H, s), 4.99 (2H, d, J=5.6Hz), 6.06 (1H, brs), 6.79 (1H, s), 7.51 (1H, t, J=8.0Hz), 7.76 (1H, d, J=8.0Hz), 8.12 (1H, d, J=8.0Hz), 8.22 (1H, s), 8.63 (1H, s)

Example 11

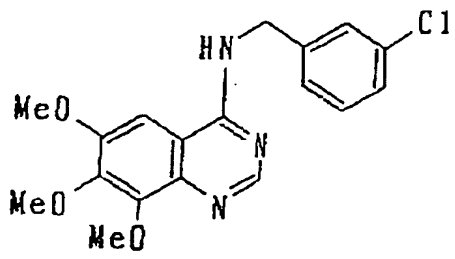
4-(4-Chlorobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{18}N_3O_3Cl$
- yield(%); 61
- m.p.(°C); 181 ~ 182
- Mass; 360 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.94 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.85 (2H, d, J=5.6Hz), 5.76 (1H, brs), 6.70 (1H, s), 7.32 (4H, brs), 8.64 (1H, s)

Example 12

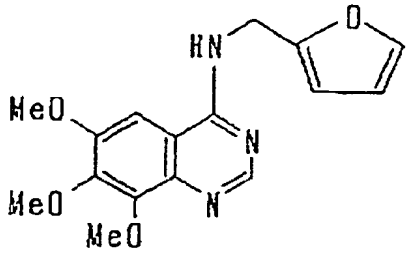
4-(3-Chlorobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{18}N_3O_3Cl$
- yield(%); 85
- m.p.(°C); 161 ~ 162
- Mass; 360 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.04 (3H, s), 4.13 (3H, s), 4.87 (2H, d, J=5.2Hz), 5.66 (1H, brs), 6.68 (1H, s), 7.29 (3H, s), 7.39 (1H, s), 8.65 (1H, s)

Example 13

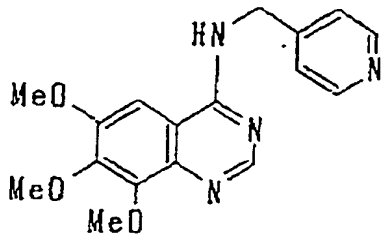
4-Furfurylamino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{16}H_{17}N_3O_4$
- yield(%); 81
- m.p.(°C); 198 ~ 199
- Mass; 316 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.87 (2H, d, J=5.2Hz), 5.67 (1H, brs), 6.37 (2H, m), 6.68 (1H, s), 7.42 (1H, s), 8.67 (1H, s)

Example 14

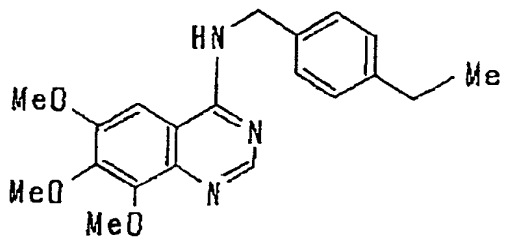
4-(4-Picolyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{17}H_{18}N_4O_3$
- yield(%); 76
- m.p.(°C); 166 ~ 168
- Mass; 327 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.05 (3H, s), 4.12 (3H, s), 4.92 (2H, d, J=6.0Hz), 6.06 (1H, brs), 6.80 (1H, s), 7.28 (2H, d, J=6.0Hz), 8.55 (2H, d, J=6.0Hz), 8.62 (1H, s)

Example 15

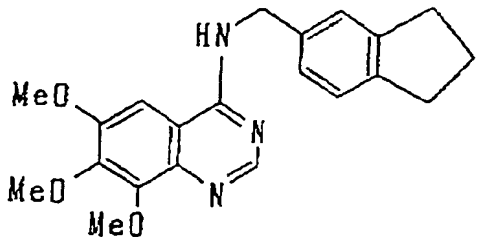
4-(4-Ethylbenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{20}H_{23}N_3O_3$
- yield(%); 88
- m.p.(°C); 195 ~ 196
- Mass; 354 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.25 (3H, t, J=7.6Hz), 2.67 (2H, q, J=7.6Hz), 3.94 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.83 (2H, d, J=4.8Hz), 5.56 (1H, brs), 6.63 (1H, s), 7.23 (2H, d, J=8.0Hz), 7.35 (2H, d, J=8.0Hz), 8.67 (1H, s)

Example 16

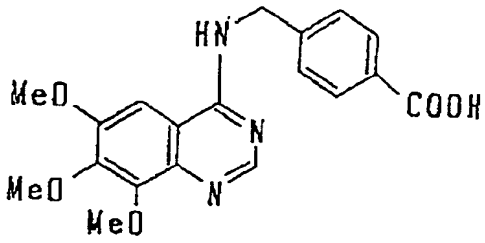
4-(Indan-5-ylmethyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{23}N_3O_3$
- yield(%); 61
- m.p.(°C); 198 ~ 199
- Mass; 366 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.11 (2H, quintet, J=7.2Hz), 2.93 (4H, t, J=7.2Hz), 3.94 (3H, s), 4.04 (3H, s), 4.14 (3H, s), 4.83 (2H, d, J=4.4Hz), 5.55 (1H, brs), 6.64 (1H, s), 7.2 ~ 7.3 (3H, m), 8.68 (1H, s)

Example 17

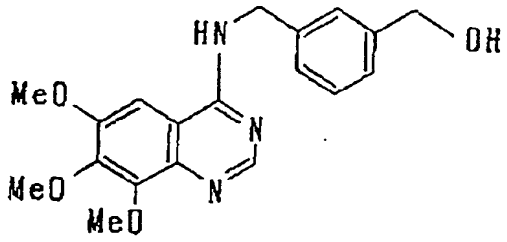
4-(4-Carboxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{19}N_3O_5$
- yield(%); 86
- m.p.(°C); 227 ~ 228 (dec.)
- Mass; 370 $(M+H)^+$
- NMR δ (DMSO-d_6):
  3.89 (3H, s), 3.92 (3H, s), 3.98 (3H, s), 4.86 (2H, d, J=5.6Hz), 7.46 (2H, d, J=8.0Hz), 7.54 (1H, s), 7.90 (2H, d, J=8.0Hz), 8.35 (1H, s), 8.67 (1H, brs)

Example 18

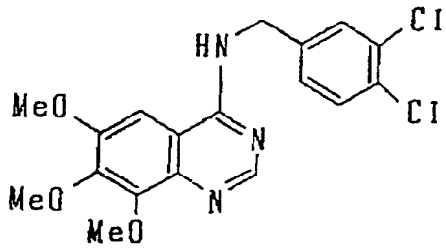
4-(3-Hydroxymethylbenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{21}N_3O_4$
- yield(%); 86
- m.p.(°C); amorphous
- Mass; 356 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.93 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.70 (2H, s), 4.86 (2H, d, J=5.2Hz), 5.82 (1H, brs), 6.72 (1H, s), 7.3 ~ 7.4 (4H, m), 8.63 (1H, s)

Example 19

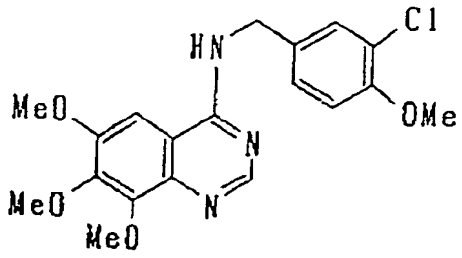
4-(3,4-Dichlorobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_3Cl_2$
- yield(%); 85
- m.p.(°C); 205 ~ 206
- Mass; 394 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.04 (3H, s), 4.12 (3H, s), 4.84 (2H, d, J=5.6Hz), 5.88 (1H, brs), 6.74 (1H, s), 7.24 (1H, d, J=8.4Hz), 7.40 (1H, d, J=8.4Hz), 7.47 (1H, s), 8.63 (1H, s)

Example 20

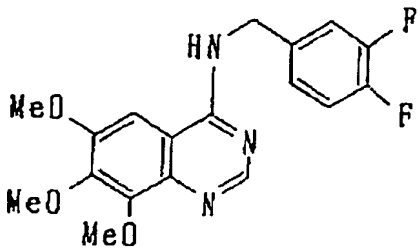
4-(3-Chloro-4-methoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{20}N_3O_4Cl$
- yield(%); 83
- m.p.(°C); 164 ~ 165
- Mass; 390 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.90 (3H, s), 3.97 (3H, s), 4.04 (3H, s), 4.13 (3H, s), 4.80 (2H, d, J=5.2Hz), 5.90 (1H, brs), 6.75 (1H, s), 6.91 (1H, d, J=8.8Hz), 7.30 (1H, dd, J=8.8 Hz, 2.0Hz), 7.43 (1H, d, J=2.0Hz), 8.65 (1H, s)

Example 21

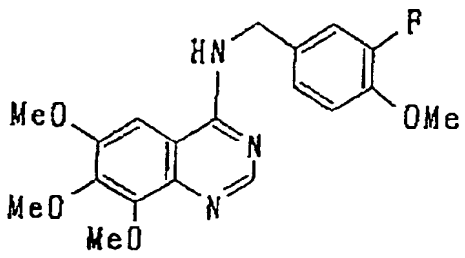
4-(3,4-Difluorobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_3F_2$
- yield(%); 96
- m.p.(°C); 175 ~ 177
- Mass; 362 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.04 (3H, s), 4.13 (3H, s), 4.85 (2H, d, J=5.2Hz), 5.73 (1H, brs), 6.69 (1H, s), 7.1 ~ 7.3 (3H, m), 8.64 (1H, s)

Example 22

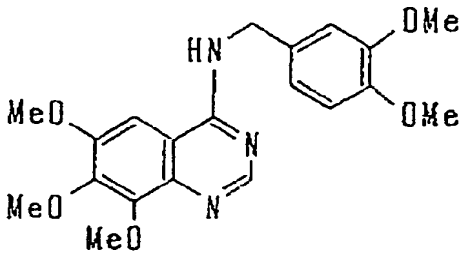
4-(3-Fluoro-4-methoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{20}N_3O_4F$
- yield(%); 82
- m.p.(°C); 171 ~ 172
- Mass; 374 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.89 (3H, s), 3.98 (3H, s), 4.04 (3H, s), 4.12 (3H, s), 4.81 (2H, d, J = 5.6Hz), 6.27 (1H, brs), 6.86 (1H, s), 6.94 (1H, m), 7.14 ~ 7.19 (2H, m), 8.64 (1H, s)

Example 23

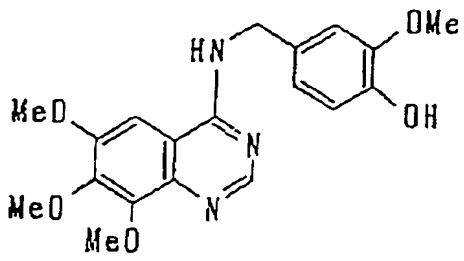
4-(3,4-Dimethoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{20}H_{23}N_3O_5$
- yield(%); 32
- m.p.(°C); 171 ~ 172
- Mass; 386 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.87 (3H, s), 3.89 (3H, s), 3.94 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.79 (2H, d, J = 5.2Hz), 5.67 (1H, brs), 6.69 (1H, s), 6.86 (1H, d, J = 8.8Hz), 6.96 (1H, s), 6.98 (1H, d, J = 8.8Hz), 8.67 (1H, s)

Example 24

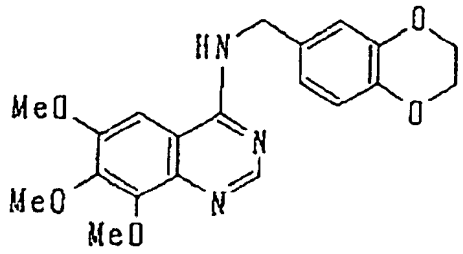
4-(4-Hydroxy-3-methoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{21}N_3O_5$
- yield(%); 16
- m.p.(°C); 201 ~ 202 (dec.)
- Mass; 372 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.88 (3H, s), 3.96 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.78 (2H, d, J=5.2Hz), 6.00 (1H, brs), 6.77 (1H, s), 6.91 (1H, s), 6.92 (1H, s), 6.97 (1H, s), 8.65 (1H, s)

Example 25

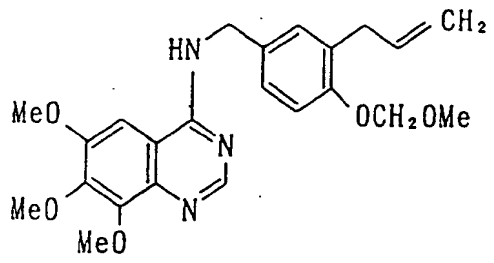
4-(3,4-Ethylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{20}H_{21}N_3O_5$
- yield(%); 92
- m.p.(°C); 217 ~ 219
- Mass: 384 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.95 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.26 (4H, s), 4.75 (2H, d, J=5.2Hz), 5.54 (1H, brs), 6.64 (1H, s), 6.87 (1H, d, J=8.0Hz), 6.90 (1H, d, J=8.0Hz), 6.94 (1H, s), 8.66 (1H, s)

Example 26

4-(3-Allyl-4-methoxymethoxybenzyl)amino-6,7,8-trimethoxyquinazoline

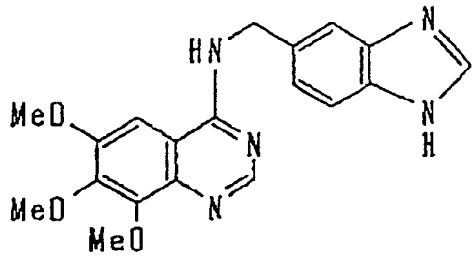


- molecular formula; $C_{23}H_{27}N_3O_5$
- yield(%); 49
- m.p.(°C); 120 ~ 121
- Mass; 426 $(M+H)^+$
- NMR δ ($CDCl_3$);

  3.41 (2H, d, J=6.8Hz), 3.48 (3H, s), 3.94 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 4.77 (2H, d, J=5.2Hz), 5.06 (2H, m), 5.21 (2H, s), 5.78 (1H, brs), 5.98 (1H, m), 6.71 (1H, s), 7.07 (1H, d, J=8.4Hz), 7.23 (1H, s), 7.24 (1H, d, J=8.4Hz), 8.65 (1H, s)

Example 27

4-(Benzimidazol-5-ylmethyl)amino-6,7,8-trimethoxyquinazoline

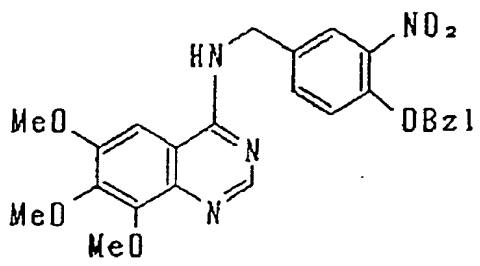


- molecular formula; $C_{19}H_{19}N_5O_3$
- yield(%); 52
- m.p.(°C); 235 ~ 240 (dec.)
- Mass; 366 $(M+H)^+$
- NMR δ (DMSO-d_6);

  3.93 (3H, s), 3.95 (3H, s), 3.98 (3H, s), 4.97 (2H, d, J=6.0Hz), 7.30 (1H, dd, J=8.4Hz, 1.6Hz), 7.57 (1H, d, J=8.4Hz), 7.63 (1H, d, J=1.6Hz), 7.83 (1H, s), 8.31 (1H, s), 8.36 (1H, brs), 8.52 (1H, s), 9.76 (1H, brs)

Example 28

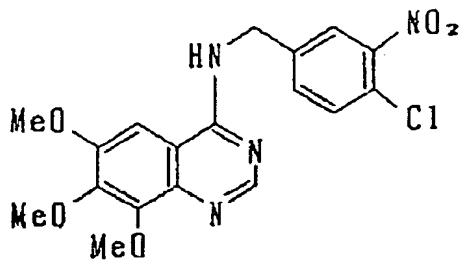
4-(4-Benzyloxy-3-nitrobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{25}H_{24}N_4O_6$
- yield(%); 81
- m.p.(°C); 181 ~ 182
- Mass; 477 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.98 (3H, s), 4.03 (3H, s), 4.10 (3H, s), 4.85 (2H, d, J=5.2Hz), 5.21 (2H, s), 6.54 (1H, brs), 6.93 (1H, s), 7.06 (1H, d, J=8.4Hz), 7.30 ~ 7.45 (5H, m), 7.60 (1H, dd, J=8.4Hz, 2.4Hz), 7.87 (1H, d, J=2.4Hz), 8.61 (1H, s)

Example 29

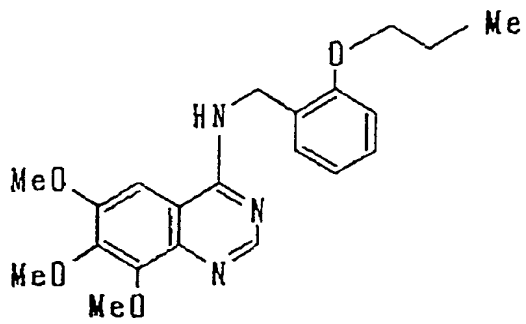
4-(4-Chloro-3-nitrobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_4O_5Cl$
- yield(%); 88
- m.p.(°C); 218 ~ 219 (dec.)
- Mass; 405 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.98 (3H, s), 4.04 (3H, s), 4.13 (3H, s), 4.93 (2H, d, J=6.0Hz), 5.98 (1H, brs), 6.75 (1H, s), 7.50 (1H, d, J=8.4Hz), 7.58 (1H, dd, J=8.4Hz, 2.0Hz), 7.87 (1H, d, J=2.0Hz), 8.61 (1H, s)

Example 30

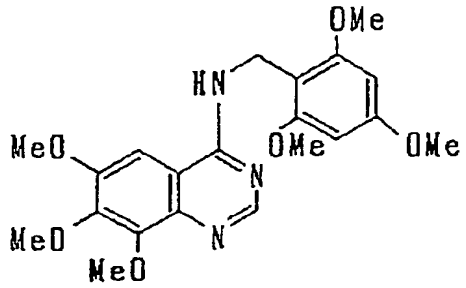
4-(2-Propoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{25}N_3O_4$
- yield(%); 80
- m.p.(°C); 139 ~ 140
- Mass; 384 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.07 (3H, t, J=7.4Hz), 1.85 (2H, m), 3.95 (3H, s), 4.02 (3H, s), 4.02 (2H, t, J=6.4Hz), 4.10 (3H, s), 4.89 (2H, d, J=5.6Hz), 6.72 (1H, s), 6.9 (2H, m), 7.28 (1H, m), 7.38 (1H, d, J=7.2Hz), 8.64 (1H, s)

Example 31

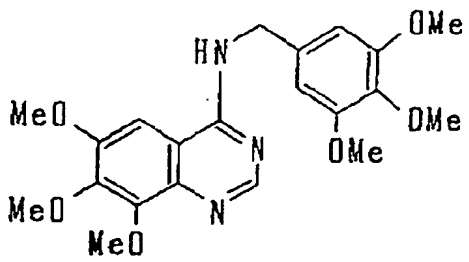
4-(2,4,6-Trimethoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{25}N_3O_6$
- yield(%); 64
- m.p.(°C); 213 ~ 215
- Mass; 416 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.85 (9H, s), 3.92 (3H, s), 4.01 (3H, s), 4.11 (3H, s), 4.79 (2H, d, J=4.4Hz), 5.65 (1H, brs), 6.20 (2H, s), 6.60 (1H, s), 8.68 (1H, s)

Example 32

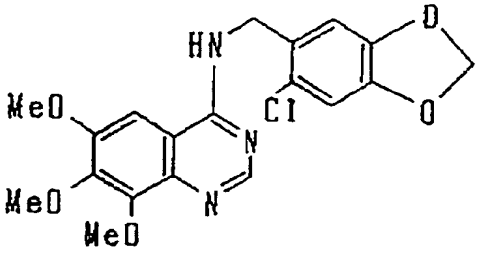
4-(3,4,5-Trimethoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{25}N_3O_6$
- yield(%); 60
- m.p.(°C); 153 ~ 154
- NMR δ ($CDCl_3$);
  3.85 (9H, s), 3.97 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.80 (2H, d, J=5.6Hz), 6.66 (2H, s), 6.80 (1H, s), 8.66 (1H, s)

Example 33

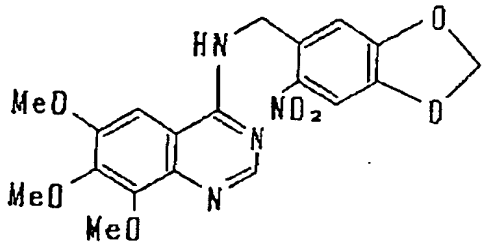
4-(2-Chloro-4,5-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{18}N_3O_5Cl$
- yield(%); 76
- m.p.(°C); 220 ~ 221
- Mass; 404 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.02 (3H, s), 4.11 (3H, s), 4.86 (2H, d, J=6.0Hz), 5.95 (2H, s), 6.70 (1H, brt, J=6.0Hz), 6.86 (1H, s), 6.95 (1H, s), 6.98 (1H, s), 8.61 (1H, s)

Example 34

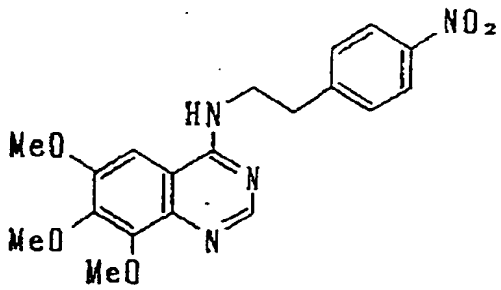
4-(4,5-Methylenedioxy-2-nitrobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{18}N_4O_7$
- yield(%); 15
- m.p.(°C); 182 ~ 183
- Mass; 415 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.99 (3H, s), 4.02 (3H, s), 4.10 (3H, s), 5.08 (2H, d, J=6.4Hz), 6.09 (2H, s), 6.82 (2H, s & brs), 7.27 (1H, s), 7.57 (1H, s), 8.61 (1H, s)

Example 35

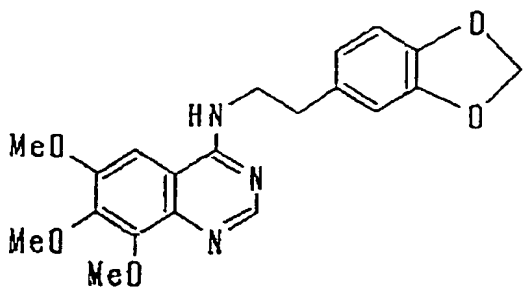
4-[2-(4-Nitrophenyl)ethyl]amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{20}N_4O_5$
- yield(%); 58
- m.p.(°C); 152 ~ 153
- Mass; 385 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.18 (2H, t, J=7.2Hz), 3.92 (3H, s), 3.96 (3H, m), 4.04 (3H, s), 4.13 (3H, s), 5.57 (1H, brs), 6.58 (1H, s), 7.41 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.8Hz), 8.66 (1H, s)

Example 36

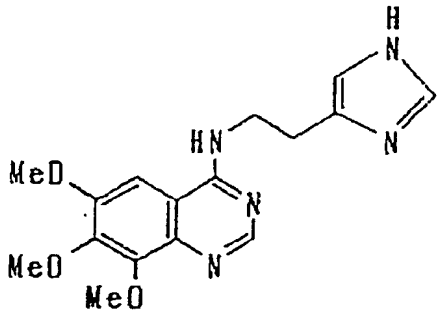
4-[2-(3,4-Methylenedioxyphenyl)ethyl]amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{20}H_{21}N_3O_5$
- yield(%); 68
- m.p.(°C); 193 ~ 194
- Mass; 384 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.96 (2H, t, J=6.8Hz), 3.87 (2H, m), 3.93 (3H, s), 4.03 (3H, s), 4.12 (3H, s), 5.43 (1H, brs), 5.95 (2H, s), 6.52 (1H, s), 6.71 (1H, d, J=8.0Hz), 6.77 (1H, s), 6.78 (1H, d, J=8.0Hz), 8.65 (1H, s)

Example 37

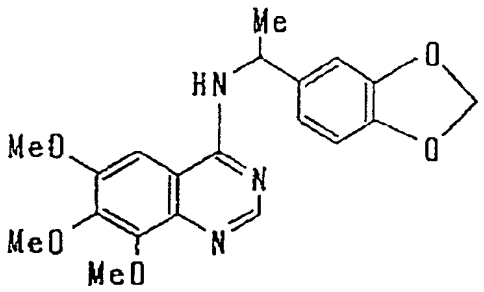
4-[2-(Imidazol-4-yl)ethyl]amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{16}H_{19}N_5O_3$
- yield(%); 77
- m.p.(°C); 164 ~ 166 (dec.)
- Mass; 330 $(M+H)^+$
- NMR δ (DMSO-d_6);
  3.00 (2H, t, J=7.2Hz), 3.81 (2H, m), 3.87 (3H, s), 3.92 (3H, s), 3.97 (3H, s), 7.25 (1H, s), 7.56 (1H, s), 8.39 (1H, s), 8.45 (1H, s), 8.50 (1H, brs)

Example 38

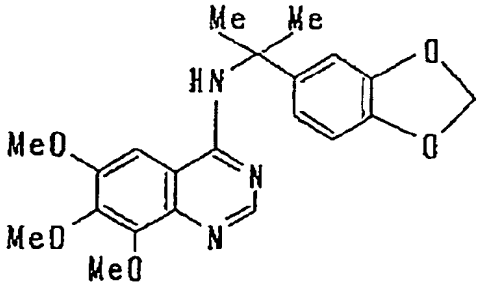
4-(α-Methyl-3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{20}H_{21}N_3O_5$
- yield(%); 67
- m.p.(°C); 200 ~ 201
- Mass; 384 $(M+H)^+$
- NMR δ (CDCl);
  1.67 (2H, d, J=6.8Hz), 3.99 (3H, s), 4.04 (3H, s), 4.13 (3H, s), 5.47 (1H, brs), 5.57 (1H, t, J=6.8Hz), 5.97 (2H, s), 6.65 (1H, s), 6.81 (1H, d, J=7.6Hz), 6.94 (1H, d, J=7.6Hz), 6.95 (1H, s), 8.63 (1H, s)

Example 39

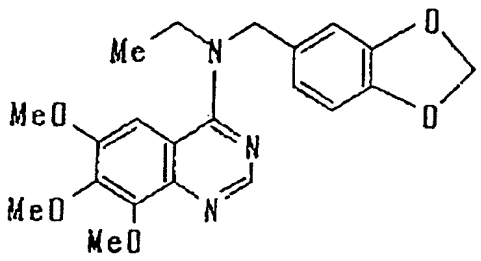
4-[1-Methyl-1-(3,4-methylenedioxyphenyl)ethyl]amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{23}N_3O_5$
- yield(%); 4
- m.p.(°C); 191 ~ 192
- Mass; 398 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.90 (6H, s), 4.03 (3H, s), 4.03 (3H, s), 4.09 (3H, s), 5.93 (2H, s), 6.74 (1H, d, J=7.6Hz), 6.82 (1H, s), 6.92 (2H, m), 8.46 (1H, s)

Example 40

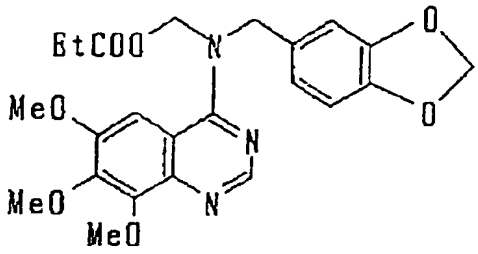
4-[N-Ethyl-(3,4-methylenedioxybenzyl)amino]-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{23}N_3O_5$
- yield(%); 73
- m.p.(°C); 100 ~ 101
- Mass; 398 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.37 (3H, t, J = 7.0Hz), 3.56 (3H, s), 3.67 (2H, q, J = 7.0Hz), 4.03 (3H, s), 4.11 (3H, s), 4.79 (2H, s), 5.98 (2H, s), 6.85 (1H, d, J = 7.2Hz), 6.93 (1H, s), 6.93 (1H, d, J = 7.2Hz), 6.97 (1H, s), 8.69 (1H, s)

Example 41

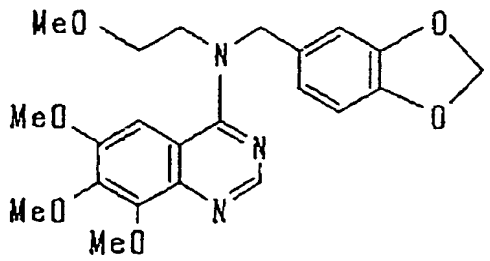
4-[N-(Ethoxycarbonylmethyl)-(3,4-methylenedioxybenzyl)amino]-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{23}H_{25}N_3O_7$
- yield(%); 41
- m.p.(°C); oily substance
- Mass; 456 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.29 (3H, t, J = 7.2Hz), 3.44 (3H, s), 4.02 (3H, s), 4.10 (3H, s), 4.20 (2H, s), 4.25 (2H, q, J = 7.2Hz), 4.98 (2H, s), 6.00 (2H, s), 6.88 (1H, d, J = 8.0Hz), 6.97 (1H, s), 7.01 (1H, d, J = 8.0Hz), 8.64 (1H, s)

Example 42

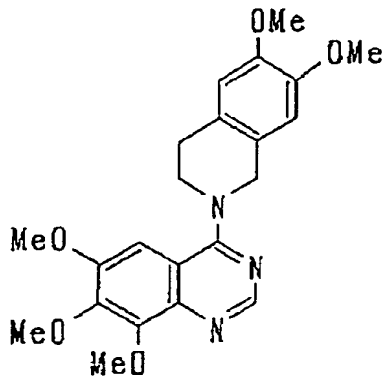
4-[N-(2-Methoxyethyl)-(3,4-methylenedioxybenzyl)amino]-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{22}H_{25}N_3O_6$
- yield(%); 21
- m.p.(°C); 87 ~ 88
- Mass; 428 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.36 (3H, s), 3.58 (3H, s), 3.80 - 3.85 (4H, m), 4.02 (3H, s), 4.10 (3H, s), 4.92 (2H, s), 5.97 (2H, s), 6.83 (1H, d, J = 7.6Hz), 6.92 (1H, d, J = 7.6Hz), 6.94 (1H, s), 7.19 (1H, s), 8.67 (1H, s)

Example 43

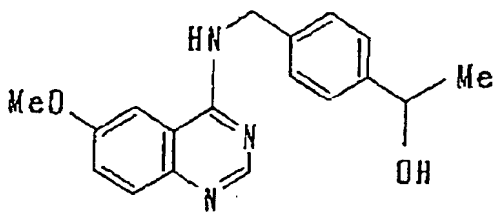
4-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{22}H_{25}N_3O_5$
- yield(%); 79
- m.p.(°C); 157 ~ 158
- Mass; 412 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.11 (2H, t, J = 5.8Hz), 3.87 (3H, s), 3.89 (3H, s), 3.96 (2H, t, J = 5.8Hz), 3.99 (3H, s), 4.07 (3H, s), 4.14 (3H, s), 4.80 (2H, s), 6.67 (1H, s), 6.71 (1H, s), 7.03 (1H, s), 8.74 (1H, s)

Example 44

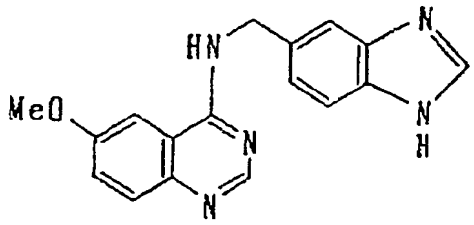
4-[4-(1-Hydroxyethyl)benzyl]amino-6-methoxyquinazoline



- molecular formula; $C_{18}H_{19}N_3O_2$
- yield(%); 46
- m.p.(°C); amorphous
- Mass; 310 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.47 (2H, d. J=6.4Hz), 3.91 (3H, s), 4.87 (2H, d, J=5.2Hz), 4.84 ~ 4.94 (1H, m), 7.34 ~ 7.42 (6H, m), 7.59 (1H, brs), 7.79 (1H, d, J=8.8Hz), 8.52 (1H, s)

Example 45

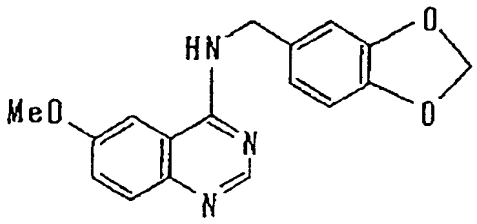
4-(Benzimidazol-5-ylmethyl)amino-6-methoxyquinazoline



- molecular formula; $C_{17}H_{15}N_5O$
- yield(%); 18
- m.p.(°C); 254 ~ 255
- Mass; 306 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.88 (3H, s), 4.91 (2H, d, J=6.0Hz), 7.24 (1H, d, J=8.4Hz), 7.40 (1H, dd, J=9.2Hz, 2.8Hz), 7.54 (1H, d, J=8.4Hz), 7.56 (1H, s), 7.63 (1H, d, J=9.2Hz), 7.73 (1H, d, J=2.8Hz), 8.16 (1H, s), 8.37 (1H, s), 8.67 (1H, t, J=6.0Hz), 12.33 (1H, brs)

Example 46

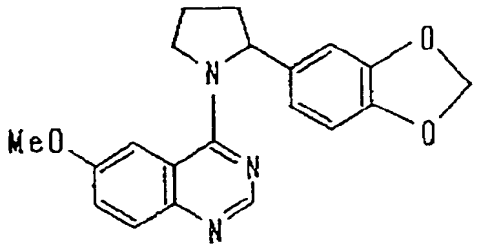
4-(3,4-Methylenedioxybenzyl)amino-6-methoxyquinazoline



- molecular formula; $C_{17}H_{15}N_3O_3$
- yield(%); 86
- m.p.(°C); 207 ~ 208
- Mass; 310 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.89 (3H, s), 4.78 (2H, d, J=5.2Hz), 5.70 (1H, brs), 5.97 (2H, s), 6.80 (1H, d, J=7.6Hz), 6.9 (3H, m), 7.40 (1H, d, J=9.2Hz), 7.80 (1H, d, J=9.2Hz), 8.63 (1H, s)

Example 47

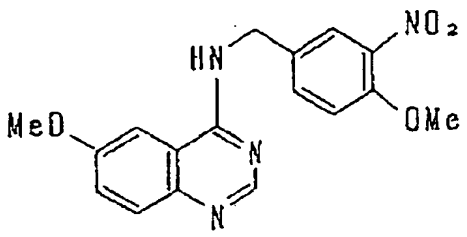
4-[2-(3,4-Methylenedioxyphenyl)pyrrolidino]-6-methoxyquinazoline



- molecular formula; $C_{20}H_{19}N_3O_3$
- yield(%); 85
- m.p.(°C); oily substance
- Mass; 350 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.95 ~ 2.10 (3H, m), 2.37 (1H, m), 3.58 (3H, s), 4.05 ~ 4.20 (2H, m), 5.58 (1H, m), 5.93 (1H, s), 5.94 (1H, s), 6.78 (1H, d, J=8.4Hz), 6.84 (1H, s), 6.85 (1H, d, J=8.4Hz), 7.30 (1H, d, J=10.0Hz), 7.35 (1H, s), 7.74 (1H, d, J=10.0Hz), 8.53 (1H, s)

Example 48

4-(4-Methoxy-3-nitrobenzyl)amino-6-methoxyquinazoline

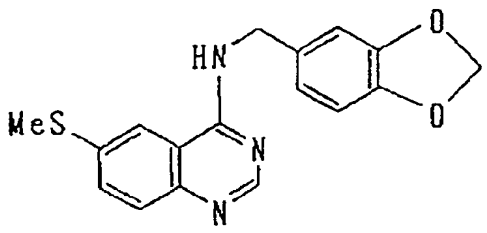


- molecular formula; $C_{17}H_{16}N_4O_4$
- yield(%); 22
- m.p.(°C); 205 ~ 206 (dec.)
- Mass; 341 $(M+1)^+$
- NMR δ ($CDCl_3$);

  3.93 (3H, s), 3.94 (3H, s), 4.91 (2H, d, J=6.0Hz), 7.07 (1H, dd, J=8.4Hz, 1.2Hz), 7.21 (1H, d, J=1.2Hz), 7.39 (1H, dd, J=9.2Hz, 2.4Hz), 7.53 (1H, d, J=2.4Hz), 7.75 (1H, d, J=9.2Hz), 7.82 (1H, d, J=8.4Hz), 8.03 (1H, brs), 8.51 (1H, s)

Example 49

4-(3,4-Methylenedioxybenzyl)amino-6-methylthioquinazoline



4.12 g (0.0196 mol) of 4-chloro-6-methylthioquinazoline, 3.70 g (0.0245 mol) of piperonylamine and 3.50 g (0.0330 mol) of sodium carbonate were mixed with 100 ml of isopropyl alcohol. The obtained mixture was heated under reflux for 24 hours and distilled under a reduced pressure to remove the solvent. The obtained residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) and recrystallized from chloroform/n-hexane to give 5.32 g of the title compound as a pale-yellow crystal.

- molecular formula; $C_{17}H_{15}O_2N_3S$
- yield(%); 83
- m.p.(°C); 174 ~ 175
- Mass; 326 $(M+H)^+$
- NMR δ ($CDCl_3$);

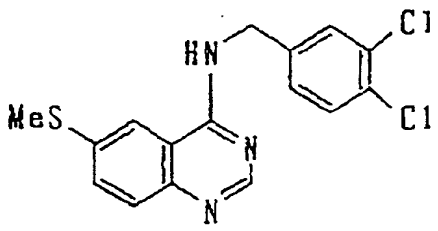
  2.59 (3H, s), 4.79 (2H, d, J=5.6Hz), 5.93 (2H, s), 6.77 (1H, d, J=8.0Hz), 6.89 (1H, d, J=8.0Hz), 6.94 (1H, s), 7.62 (1H, dd, J=8.8Hz, 2.0Hz), 7.75 (1H, d, J=8.8Hz), 7.97 (1H, d, J=2.0Hz), 8.10 (1H, brs), 8.56 (1H, s)

Examples 50 to 54

The following compounds were prepared in a similar manner to that of Example 49.

Example 50

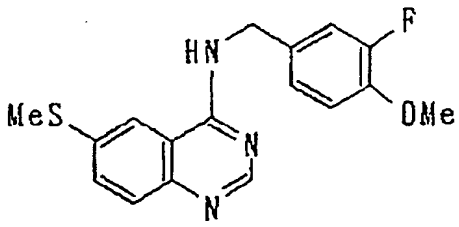
4-(3,4-Dichlorobenzyl)amino-6-methylthioquinazoline



- molecular formula; $C_{16}H_{13}N_3SCl_2$
- yield(%); 85
- m.p.(°C); 184 ~ 185
- Mass; 350 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.61 (3H, s), 4.83 (2H, d, J=5.6Hz), 7.28 (1H, dd, J=8.4Hz, 2.0Hz), 7.40 (1H, d, J=8.4Hz), 7.51 (1H, d, J=2.0Hz), 7.64 (1H, dd, J=8.8Hz, 2.0Hz), 7.76 (1H, d, J=8.8Hz), 7.97 (1H, d, J=2.0Hz), 8.19 (1H, brs), 8.55 (1H, s)

Example 51

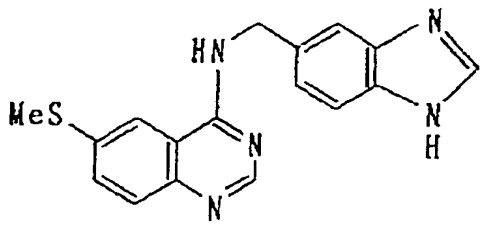
4-(3-Fluoro-4-methoxybenzyl)amino-6-methylthioquinazoline



- molecular formula; $C_{17}H_{16}N_3OSF$
- yield(%); 89
- m.p.(°C); 168 ~ 169
- Mass; 330 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.58 (3H, s), 3.90 (3H, s), 4.82 (2H, d, J=5.6Hz), 6.29 (1H, brs), 6.95 (1H, m), 7.13 ~7.18 (2H, m), 7.54 (1H, s), 7.63 (1H, d, J=8.8Hz), 7.79 (1H, d, J=8.8Hz), 8.64 (1H, s)

Example 52

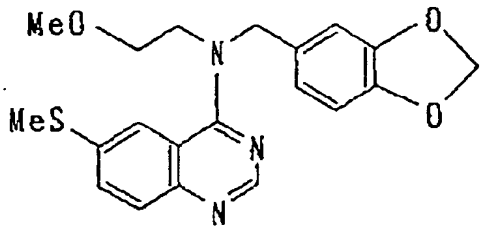
4-(Benzimidazol-5-ylmethyl)amino-6-methylthioquinazoline



- molecular formula; $C_{17}H_{15}N_5S$
- yield(%); 48
- m.p.(°C); 271 ~ 275 (dec.)
- Mass; 322 $(M+H)^+$
- NMR δ (DMSO-d_6);
  2.67 (3H, s), 5.06 (2H, d, J = 5.6Hz), 7.47 (1H, d, J = 8.4Hz), 7.68 (1H, d, J = 8.8Hz), 7.77 (2H, m), 7.87 (1H, d, J = 8.8Hz), 8.40 (1H, s), 8.77 (1H, s), 8.84 (1H, s), 10.68 (1H, brs)

Example 53

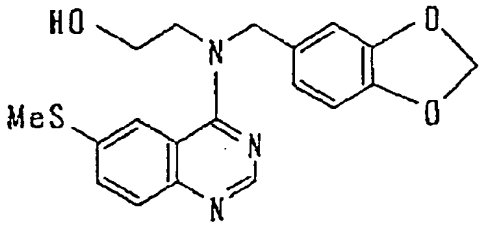
4-[N-(2-Methoxyethyl)-(3,4-methylenedioxybenzyl)amino]-6-methylthioquinazoline



- molecular formula; $C_{20}H_{21}N_3O_3S$
- yield(%); 27
- m.p.(°C); 92 ~ 93
- Mass; 384 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.16 (3H, s), 3.35 (3H, s), 3.82 (2H, t, J = 5.0Hz), 3.89 (2H, t, J = 5.0Hz), 5.01 (2H, s), 5.98 (2H, s), 6.84 (1H, d, J = 8.4Hz), 6.89 (1H, d, J = 8.4Hz), 6.90 (1H, s), 7.56 (1H, dd, J = 8.8Hz, 2.0Hz), 7.66 (1H, d, J = 2.0Hz), 7.82 (1H, d, J = 8.8Hz)

Example 54

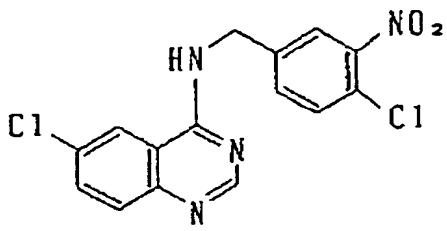
4-[N-(2-Hydroxyethyl)-(3,4-methylenedioxybenzyl)amino]-6-methylthioquinazoline



- molecular formula; $C_{19}H_{19}N_3O_3S$
- yield(%); 21
- m.p.(°C); 146 ~ 147 (dec.)
- Mass; 370 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.00 (3H, s), 3.93 (2H, t, J=4.2Hz), 4.01 (2H, t, J=4.2Hz), 5.00 (2H, s), 6.01 (2H, s), 6.89 (3H, m), 7.57 (2H, m), 7.82 (1H, d, J=9.2Hz), 8.55 (1H, s)

Example 55

4-(4-Chloro-3-nitrobenzyl)amino-6-chloroquinazoline

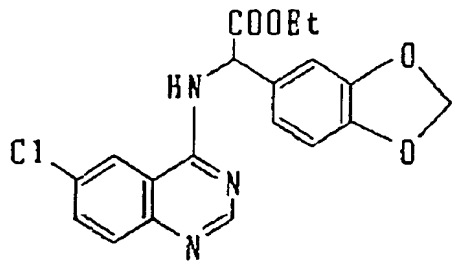


3.00 g (0.015 mol) of 4,6-dichloroquinazoline and 3.80 g (0.0170 mol) of 4-chloro-3-nitrobenzylamine hydrochloride were dissolved in a mixture comprising 100 ml of isopropyl alcohol and 15 ml of triethylamine. The obtained solution was heated under reflux for 24 hours and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (chloroform/ethyl acetate) and recrystallized from chloroform/n-hexane to give 4.85 g of the title compound as a pale-yellow crystal.

- molecular formula; $C_{15}H_{10}N_4O_2Cl_2$
- yield(%); 92
- m.p.(°C); 199 ~ 200
- Mass; 349 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.85 (2H, d, J=6.0Hz), 7.49 (1H, d, J=8.4Hz), 7.61 (1H, dd J=8.4Hz, 2.0Hz), 7.66 (1H, dd, J=8.8Hz, 2.0Hz), 7.76 (1H, d, J=8.8Hz), 7.96 (1H, d, J=2.0Hz), 8.20 (1H, d, J=2.0Hz), 8.23 (1H, brt, J=6.0Hz), 8.58 (1H, s)

Example 56

4-(α-Ethoxycarbonyl-3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



30 ml of 2-propanol, 1.07 g of triethylamine and 1.01 g of α-ethoxycarbonyl-3,4-methylenedioxybenzylamine were added to 704 mg of 4,6-dichloroquinazoline. The obtained mixture was refluxed for 4 hours, followed by the addition of water. The obtained mixture was extracted with chloroform thrice. The chloroform layers were combined, dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue was recrystallized (from ethanol/ethyl acetate/hexane) to give 1.167 g of the title compound.

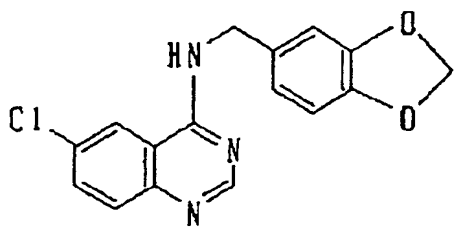
- molecular formula; $C_{19}H_{16}N_3O_4Cl$
- yield(%); 86
- m.p.(°C); 169 ~ 170
- Mass m/e; 386 (M+1)
- NMR δ ($CDCl_3$);
  1.28 (3H, t, J=7.2Hz), 4.27 (2H, m), 5.85 (1H, d, J=6.4Hz), 5.98 (2H, s), 6.70 (1H, brs), 6.81 (1H, d, J=8.8Hz), 6.99 (2H, m), 7.10 (1H, dd, J=8.8Hz, 2.4Hz), 7.83 (1H, d, J=2.4Hz), 8.85 (1H, d, J=8.8Hz), 8.63 (1H, s)

Examples 57 to 64

The following compounds were prepared in a similar manner to that of Example 56 or 57.

Example 57

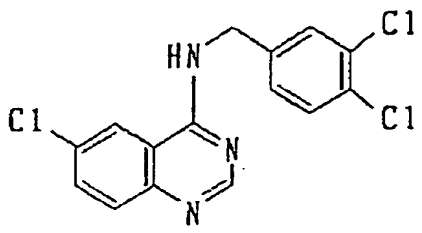
4-(3,4-Methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{16}H_{12}N_3O_2Cl$
- yield(%); 76
- m.p.(°C); 199 ~ 200
- Mass; 314 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.76 (2H, d, J=5.6Hz), 5.82 (1H, brs), 5.98 (2H, s), 6.81 (1H, d, J=8.0Hz), 6.87 (1H, d, J=8.0Hz), 6.89 (1H, s), 7.67 (1H, s), 7.69 (1H, d, J=8.0Hz), 7.81 (1H, d, J=8.0Hz), 8.70 (1H, s)

Example 58

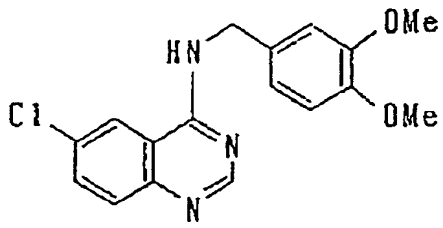
4-(3,4-Dichlorobenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{15}H_{10}N_3Cl_3$
- yield(%); 72
- m.p.(°C); 215 ~ 216
- Mass; 338 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.85 (2H, d, J = 5.6Hz), 5.94 (1H, brs), 7.24 (1H, d, J = 8.4Hz), 7.43 (1H, d, J = 8.4Hz), 7.70 (1H, d, J = 9.2Hz), 7.72 (1H, s), 7.83 (1H, d, J = 9.2Hz), 8.68 (1H, s)

Example 59

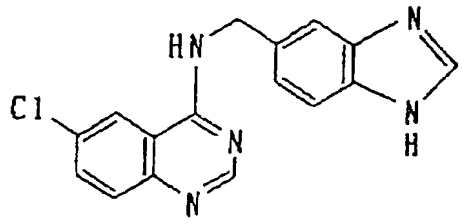
4-(3,4-Dimethoxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{17}H_{16}N_3O_2Cl$
- yield(%); 73
- m.p.(°C); 174 ~ 175
- Mass; 330 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.87 (6H, s), 4.78 (2H, d, J = 5.2Hz), 6.85 (1H, d, J = 8.0Hz), 6.96 (1H, d, J = 8.0Hz), 6.98 (1H, s), 7.34 (1H, brs), 7.65 (1H, dd, J = 9.2Hz, 2.0Hz), 7.78 (1H, d, J = 9.2Hz), 8.08 (1H, d, J = 2.0Hz), 8.65 (1H, s)

Example 60

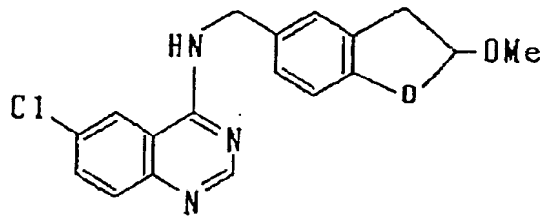
4-(Benzimidazol-5-ylmethyl)amino-6-chloroquinazoline



- molecular formula; $C_{16}H_{12}N_5Cl$
- yield(%); 76
- m.p.(°C); 243 ~ 244 (dec.)
- Mass; 310 $(M+H)^+$
- NMR δ (DMSO-d_6);
  4.89 (2H, d, J = 5.6Hz), 7.27 (1H, d, J = 8.4Hz) 7.55 (1H, d, J = 8.4Hz), 7.59 (1H, s), 7.72 (1H, d, J = 8.8Hz), 7.80 (1H, dd, J = 8.8Hz, 2.4Hz), 8.25 (1H, s), 8.50 (1H, s), 8.53 (1H, d, J = 2.4Hz), 9.07 (1H, brt, J = 5.6Hz)

Example 61

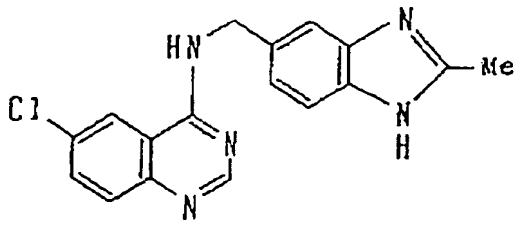
4-(2-Methoxy-2,3-dihydrobenzofuran-5-yl)methylamino-6-chloroquinazoline



- molecular formula; $C_{18}H_{16}N_3O_2Cl$ (341.798)
- yield(%); 53
- m.p.(°C); 178 ~ 179
- Mass; 342 $(MH)^+$
- NMR δ (DMSO-d_6);
  2.88 (1H, dd, J = 2.0Hz, 17.0Hz), 3.28 ~ 3.34 (1H, m), 4.68 (1H, d, J = 5.7Hz), 5.68 (1H, dd, J = 2.0Hz, 6.6Hz), 6.79 (1H, d, J = 8.2Hz), 7.14 (1H, d, J = 8.2Hz), 7.24 (1H, s), 7.70 (1H, d, J = 9.0Hz), 7.79 (1H, dd, J = 2.2Hz, 9.0Hz), 8.46 (1H, d, J = 2.2Hz), 8.48 (1H, s), 8.82 (1H, t, J = 5.7Hz)

Example 62

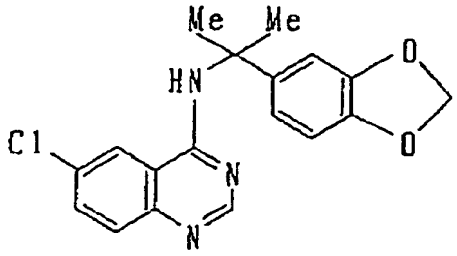
4-(2-Methylbenzimidazol-5-ylmethyl)amino-6-chloroquinazoline



- molecular formula; $C_{17}H_{14}N_5Cl$
- yield(%); 17
- m.p.(°C); 273 ~ 274 (dec.)
- Mass; 324 $(M+H)^+$
- NMR δ (DMSO-d_6);
  2.71 (3H, s), 4.94 (2H, d, J = 5.6Hz), 7.48 (1H, d, J = 8.4Hz), 7.63 (1H, d, J = 8.4Hz), 7.70 (1H, s), 7.77 (1H, d, J = 8.8Hz), 7.86 (1H, dd, J = 8.8Hz, 2.0Hz), 8.58 (1H, s), 8.65 (1H, d, J = 2.0Hz), 9.65 (1H, brs)

Example 63

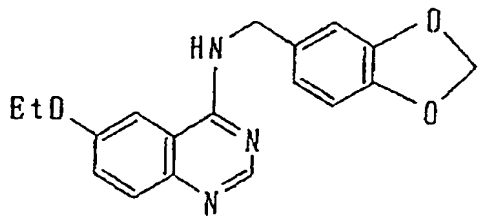
4-[1-Methyl-1-(3,4-methylenedioxyphenyl)ethyl]amino-6-chloroquinazoline



- molecular formula; $C_{18}H_{16}N_3O_2Cl$
- yield(%); 32
- m.p.(°C); 175 ~ 176
- Mass; 342 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.92 (6H, s), 5.95 (2H, s), 6.14 (1H, brs), 6.76 (1H, d, J = 7.6Hz), 6.92 (1H, d, J = 7.6Hz), 6.93 (1H, s), 7.67 (1H, dd, J = 8.8Hz), 7.77 (1H, d, J = 2.0Hz), 7.86 (1H, d, J = 8.8Hz), 8.50 (1H, s)

Example 64

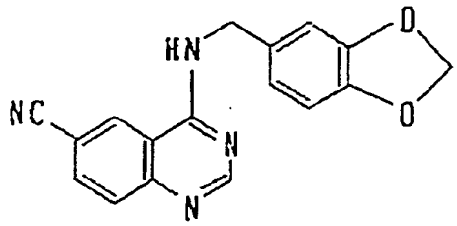
4-(3,4-Methylenedioxybenzyl)amino-6-ethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_3$
- yield(%); 44
- m.p.(°C); 190 ~ 191
- Mass; 324 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.46 (3H, t, J=6.8Hz), 4.10 (2H, q, J=6.8Hz), 4.77 (2H, d, J=5.2Hz), 5.68 (1H, brs), 5.97 (2H, s), 6.80 (1H, d, J=8.0Hz), 6.87 ~ 6.92 (3H, m), 7.39 (1H, dd, J=9.2Hz, 2.8Hz), 7.79 (1H, d, J=9.2Hz), 8.62 (1H, s)

Example 65

4-(3,4-Methylenedioxybenzyl)amino-6-cyanoquinazoline



15 ml of isopropyl alcohol, 75 mg of triethylamine and 125 mg of piperonylamine were added to 140 mg of 4-chloro-6-cyanoquinazoline. The obtained mixture was heated under reflux for 5 hours and filtered to recover a precipitate. This precipitate was introduced to a silica gel column, followed by eluting with ethyl acetate to give 200 mg of the title compound.

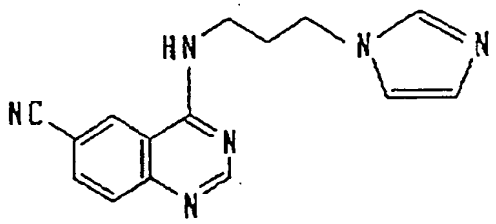
- molecular formula; $C_{17}H_{12}N_4O_2$
- yield(%); 89
- m.p.(°C); 243 ~ 244
- Mass; 305 $(M+1)^+$
- NMR δ (DMSO-d_6);
  4.67 (2H, d, J=5.6Hz), 5.96 (2H, s), 6.84 (2H, s), 6.95 (1H, s), 7.77 (1H, d, J=8.4Hz), 8.56 (1H, s), 8.89 (1H, s), 9.04 (1H, br)

Examples 66 to 87

The following compounds were prepared in a similar manner to that of Example 65.

Example 66

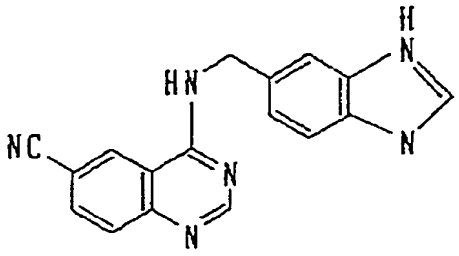
4-[3-(1-Imidazolyl)propyl]amino-6-cyanoquinazoline



- molecular formula; $C_{15}H_{14}N_6$
- yield(%); 22
- m.p.(°C); 196 ~ 197
- Mass m/e; 279 (M + 1)
- NMR δ ($CDCl_3$);
  2.27 (2H, quintet, J = 6.4Hz), 3.66 (2H, q, J = 6.4Hz), 4.17 (2H, t, J = 6.4Hz), 7.07 (1H, s), 7.11 (1H, s), 7.82 (1H, s), 7.82 (1H, s), 8.09 (1H, s), 8.37 (1H, brs), 8.66 (1H, s), 8.84 (1H, s)

Example 67

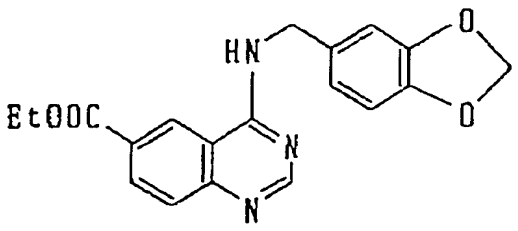
4-(Benzimidazol-5-yl)methylamino-6-cyanoquinazoline



- molecular formula; $C_{17}H_{12}N_6$
- yield(%); 68
- m.p.(°C); 274 ~ 277
- Mass; 301 $(M + 1)^+$
- NMR δ ($DMSO\text{-}d_6$);
  4.88 (2H, d, J = 5.6Hz), 7.21 ~ 7.24 (1H, m), 7.35 ~ 7.76 (2H, m), 7.78 (1H, d, J = 8.8Hz), 7.06 (1H, dd, J = 8.8Hz, 1.6Hz), 8.15 (1H, s), 8.57 (1H, s), 8.92 (1H, s), 9.14 (1H, m), 12.32 (1H, m)

Example 68

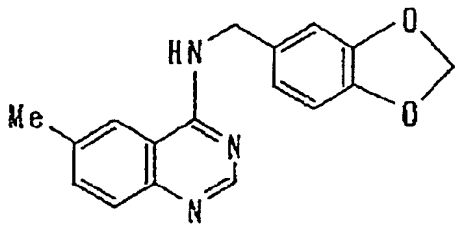
4-(3,4-Methylenedioxybenzyl)amino-6-ethoxycarbonylquinazoline



- molecular formula; $C_{19}H_{17}N_3O_4$
- yield(%); 48
- m.p.(°C); 156 ~ 157
- Mass; 352 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.43 (3H, t, J=7.2Hz), 4.44 (2H, q, J=7.2Hz), 4.79 (2H, d, J=5.2Hz), 5.98 (2H, s), 6.14 (1H, brs), 6.82 (1H, d, J=8.0Hz), 6.89 (1H, d, J=8.0Hz), 6.90 (1H, s), 7.87 (1H, d, J=8.8Hz), 8.33 (1H, d, J=8.8Hz), 8.46 (1H, s), 8.74 (1H, s)

Example 69

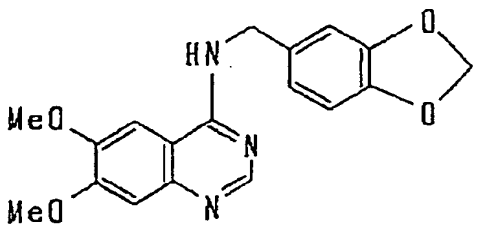
4-(3,4-Methylenedioxybenzyl)amino-6-methylquinazoline



- molecular formula; $C_{17}H_{15}N_3O_2$
- yield(%); 68
- m.p.(°C); 203 ~ 204
- Mass; 294 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.49 (3H, s), 4.76 (2H, d, J=5.6Hz), 5.79 (1H, brs), 5.96 (2H, s), 6.81 (1H, d, J=8.0Hz), 6.88 (1H, d, J=8.0Hz), 6.91 (1H, s), 7.44 (1H, s), 7.57 (1H, d, J=8.4Hz), 7.76 (1H, d, J=8.4Hz), 8.66 (1H, s)

Example 70

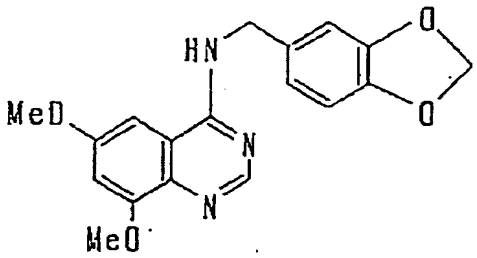
4-(3,4-Methylenedioxybenzyl)amino-6,7-dimethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_4$
- yield(%); 77
- m.p.(°C); 221 ~ 222
- Mass; 340 $(M+H)^+$
- NMR δ (DMSO-d_6);
  3.88 (3H, s), 3.89 (3H, s), 4.68 (2H, d, J=6.0Hz), 5.97 (2H, s), 6.85 (2H, s), 6.94 (1H, s), 7.09 (1H, s), 7.64 (1H, s), 8.33 (1H, s), 8.37 (1H, t, J=6.0Hz)

Example 71

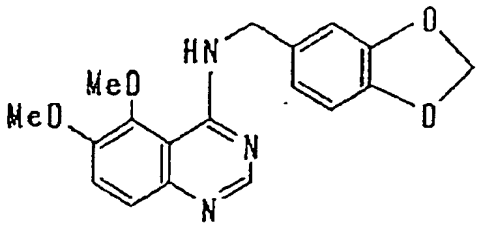
4-(3,4-Methylenedioxybenzyl)amino-6,8-dimethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_4$
- yield(%); 88
- m.p.(°C); 217 ~ 218
- Mass; 340 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.89 (3H, s), 4.01 (3H, s), 4.77 (2H, d, J=5.2Hz), 5.63 (1H, brs), 5.97 (2H, s), 6.42 (1H, d, J=2.4Hz), 6.77 (1H, d, J=2.4Hz), 6.80 (1H, d, J=7.6Hz), 6.88 (1H, dd, J=7.6Hz, 1.6Hz), 6.92 (1H, d, J=1.6Hz), 8.65 (1H, s)

Example 72

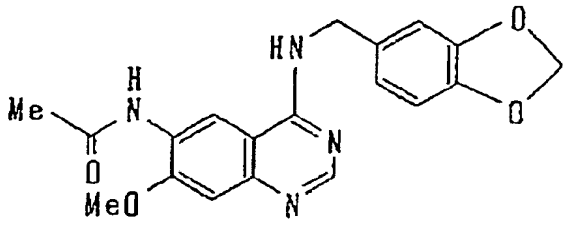
4-(3,4-Methylenedioxybenzyl)amino-5,6-dimethoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_4$
- yield(%); 74
- m.p.(°C); 122 ~ 123
- Mass; 340 $(M+1)^+$
- NMR δ ($CDCl_3$);
  3.97 (6H, s), 4.77 (2H, d, J=5.2Hz), 5.97 (2H, s), 6.81 (1H, d, J=8.0Hz), 6.86 (1H, dd, J=8.0Hz, 1.6Hz), 6.88 (1H, d, J=1.6Hz), 7.49 (1H, d, J=8.8Hz), 7.82 (1H, d, J=8.8Hz), 8.51 (1H, s), 8.64 (1H, brs)

Example 73

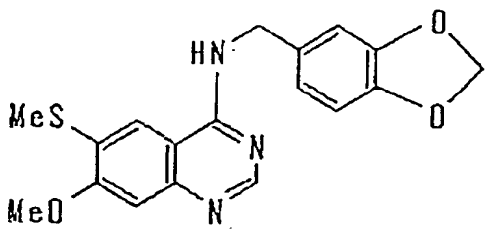
4-(3,4-Methylenedioxybenzyl)amino-6-acetamido-7-methoxyquinazoline



- molecular formula; $C_{19}H_{18}N_4O_4$
- yield(%); 66
- m.p.(°C); 164 ~ 165
- Mass; 367 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.26 (3H, s), 4.04 (3H, s), 4.76 (2H, d, J=5.6Hz), 5.95 (2H, s), 6.22 (1H, brs), 6.77 (1H, d, J=8.0Hz), 6.85 (1H, d, J=8.0Hz), 6.89 (1H, s), 7.31 (1H, s), 8.02 (1H, brs), 8.59 (1H, s), 8.81 (1H, s)

Example 74

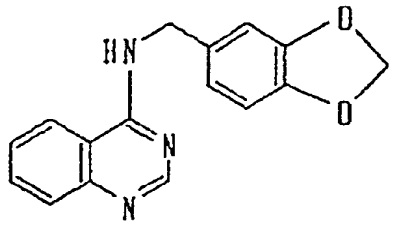
4-(3,4-Methylenedioxybenzyl)amino-6-methylthio-7-methoxyquinazoline



- molecular formula; $C_{18}H_{17}N_3O_3S$
- yield(%); 39
- m.p.(°C); 200 ~ 205 (dec.)
- Mass; 356 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.50 (3H, s), 4.01 (3H, s), 4.78 (2H, d, J=5.6Hz), 5.95 (2H, s), 6.13 (1H, brs), 6.79 (1H, d, J=8.0Hz), 6.88 (1H, d, J=8.0Hz), 6.91 (1H, s), 7.15 (1H, s), 7.33 (1H, s), 8.56 (1H, s)

Example 75

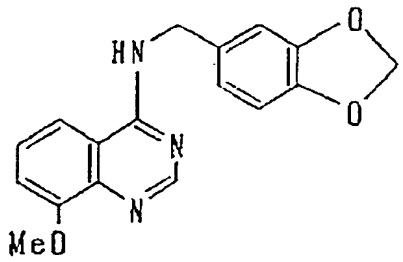
4-(3,4-Methylededioxybenzyl)aminoquinazoline



- molecular formula; $C_{15}H_{13}N_3O_2$
- yield(%); 69
- m.p.(°C); 197 ~ 198
- Mass; 280 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.78 (2H, d, J=5.2Hz), 5.85 (1H, brs), 5.96 (2H, s), 6.80 (1H, d, J=8.0Hz), 6.88 (1H, d, J=8.0Hz), 6.91 (1H, s), 7.46 (1H, t, J=8.0Hz), 7.68 (1H, d, J=8.0Hz), 7.75 (1H, t, J=8.0Hz), 7.87 (1H, d, J=8.0Hz), 8.71 (1H, s)

Example 76

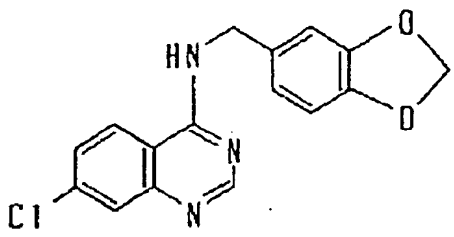
4-(3,4-Methylededioxybenzyl)amino-8-methoxyquinazoline



- molecular formula; $C_{17}N_{15}N_3O_3$
- yield(%); 76
- m.p.(°C); 195 ~ 196
- Mass; 310 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.03 (3H, s), 4.78 (2H, d, J=5.6Hz), 5.94 (2H, s), 6.77 (1H, d, J=8.0Hz), 6.89 (1H, d, J=8.0Hz), 6.92 (1H, s), 6.95 (1H, brs), 7.12 (1H, d, J=8.0Hz), 7.39 (1H, t, J=8.0Hz), 7.48 (1H, d, J=8.0Hz), 8.70 (1H, s)

Example 77

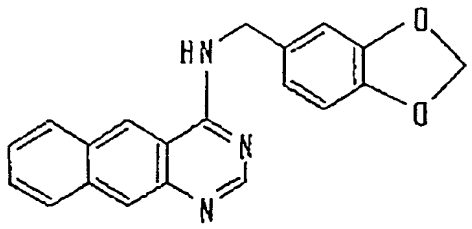
4-(3,4-Methylenedioxybenzyl)amino-7-chloroquinazoline



- molecular formula; $C_{21}H_{22}N_3O_2Cl$
- yield(%); 62
- m.p.(°C); 209 ~ 210
- Mass; 314 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.77 (2H, d, J=5.6Hz), 5.95 (2H, s), 6.78 (1H, d, J=8.0Hz), 6.88 (1H, d, J=8.0Hz), 6.92 (1H, s), 7.39 (1H, dd, J=8.8Hz, 2.0Hz), 7.4 (1H, brs), 7.83 (1H, d, J=2.0Hz), 7.96 (1H, d, J=8.8Hz), 8.63 (1H, s)

Example 78

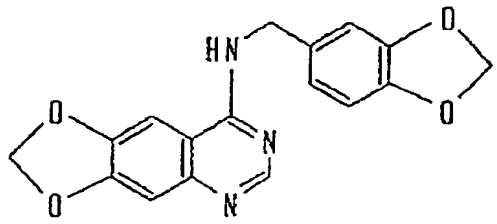
4-(3,4-Methylenedioxybenzyl)aminobenzo[g]quinazoline



- molecular formula; $C_{20}H_{15}N_3O_2$ (329)
- yield(%); 45
- m.p.(°C); 265 (dec.)
- Mass; 330 $(M+1)^+$
- NMR δ (DMSO-d_6);
  4.92 (2H, d, J=6.0Hz), 5.97 (2H, s), 6.88 (1H, d, J=8.0Hz), 6.94 (1H, dd, J=8.0Hz, 1.6Hz), 7.06 (1H, d, J=1.6Hz), 7.68 ~ 7.81 (2H, m), 8.11 (1H, d, J=8.4Hz), 8.21 (1H, d, J=8.4Hz), 8.33 (1H, s), 8.90 (1H, s), 9.36 (1H, s), 11.09 (1H, br)

Example 79

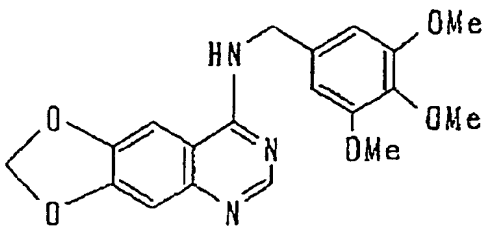
4-(3,4-Methylenedioxybenzyl)amino-6,7-methylenedioxyquinazoline



- molecular formula; $C_{17}H_{13}N_3O_4$ (323)
- yield(%); 55
- m.p.(°C); 229 ~ 231
- Mass; 324 $(M+1)^+$
- NMR δ (DMSO-d_6);
  4.62 (2H, d, J=5.6Hz), 5.94 (2H, s), 6.16 (2H, s), 6.79 (1H, d, J=8.0Hz), 6.82 (1H, dd, J=8.0Hz, 2.0Hz), 6.89 (1H, d, J=2.0Hz), 7.06 (1H, s), 7.68 (1H, s), 8.26 (1H, brt, J=5.6Hz), 8.28 (1H, s)

Example 80

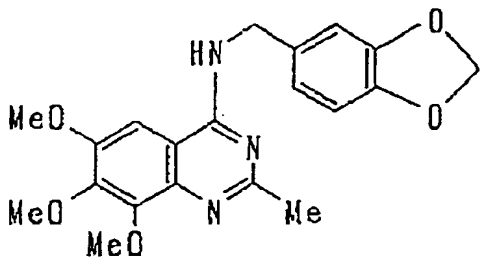
4-(3,4,5-Trimethoxybenzyl)amino-6,7-methylenedioxyquinazoline



- molecular formula; $C_{19}H_{19}N_3O_5$ (369)
- yield(%); 59
- m.p.(°C); 240 ~ 241
- Mass; 370 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.61 (3H, s), 3.70 (6H, s), 4.65 (2H, d, J=6.0Hz), 6.16 (2H, s), 6.675 (2H, s), 7.06 (1H, s), 7.72 (1H, s), 8.23 (1H, brt, J=6.0Hz), 8.30 (1H, s)

Example 81

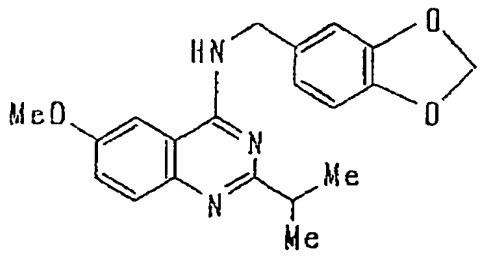
2-Methyl-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{20}H_{21}N_3O_5$
- yield(%); 58
- m.p.(°C); 190 ~ 191
- Mass; 384 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.67 (3H, s), 3.93 (3H, s), 4.01 (3H, s), 4,11 (3H, s), 4.77 (2H, d, J=5.2Hz), 5.96 (2H, s), 6.70 (1H, s) 6.79 (1H, d, J=7.6Hz), 6.89 (1H, d, J=7.6Hz), 6.93 (1H, s)

Example 82

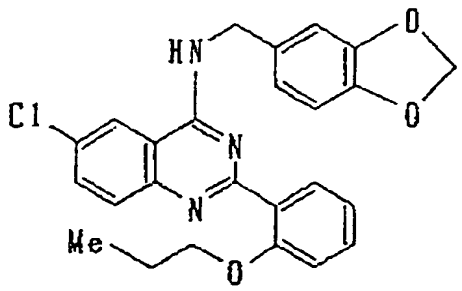
2-Isopropyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



- molecular formula; $C_{20}H_{21}N_3O_3$
- yield(%); 84
- m.p.(°C); 157 ~ 158
- Mass; 352 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.36 (6H, d, J=6.8Hz), 3.15 (1H, septet, J=6.8Hz), 3.88 (3H, s), 4.81 (2H, d, J=5.6Hz), 5.94 (2H, s), 6.78 (1H, d, J=8.0Hz), 6.91 (1H, dd, J=8.0Hz, 2.0Hz), 6.96 (1H, d, J=2.0Hz), 6.99 (1H, brd, J=2.4Hz), 7.32 (1H, dd, J=9.2Hz, 2.4Hz), 7.79 (1H, d, J=9.2Hz)

Example 83

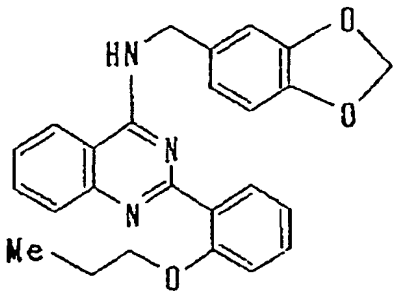
2-(2-Propoxyphenyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{25}H_{22}N_3O_3Cl$
- yield(%); 20
- m.p.(°C); 208 ~ 209
- Mass; 446 $(M+1)^+$
- NMR δ ($CDCl_3$);
  0.97 (3H, t, J=7.6Hz), 1.71 ~ 1.81 (2H, m), 4.01 (2H, t, J=6.4Hz), 4.81 (2H, brs), 5.80 (1H, br), 5.96 (2H, s), 6.79 ~ 7.86 (10H, m)

Example 84

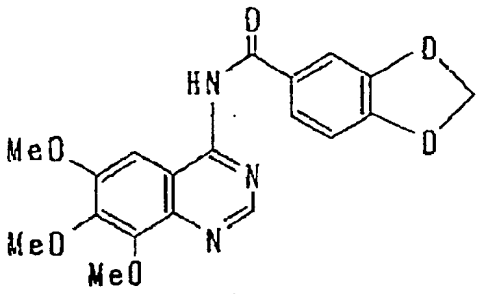
2-(2-Propoxyphenyl)-4-(3,4-methylenedioxybenzyl)aminoquinazoline



- molecular formula; $C_{25}H_{23}N_3O_3$ (413)
- yield(%); 15
- m.p.(°C); 130 ~ 131
- Mass; 414 $(M+1)^+$
- NMR δ ($CDCl_3$);
  0.96 (3H, t, J=7.2Hz), 1.71 ~ 1.77 (2H, m), 4.00 (2H, t, J=6.4Hz), 4.83 (2H, s), 5.95 (2H, s), 6.77 ~ 7.93 (12H, m)

Example 85

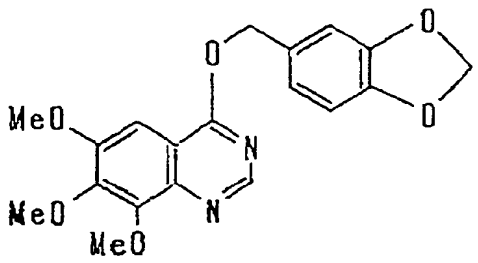
4-(3,4-Methylenedioxybenzamido)-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{17}N_3O_6$
- yield(%); 13
- m.p.(°C); 190 ~ 192
- Mass; 384 $(M+H)^+$
- NMR δ ($CDCl_3$);
  4.10 (6H, s), 4.12 (3H, s), 6.07 (2H, s), 6.91 (1H, d, J=8.0Hz), 7.86 (1H, s), 7.90 (1H, s), 8.06 (1H, d, J=8.0Hz), 8.18 (1H, s)

Example 86

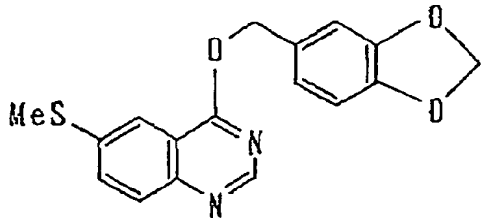
4-(3,4-Methylenedioxybenzyl)oxy-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{18}N_2O_6$
- yield(%); 49
- m.p.(°C); 141 ~ 142
- Mass; 371 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.97 (3H, s), 4.05 (3H, s), 4.13 (3H, s), 5.53 (2H, s), 5.99 (2H, s), 6.84 (1H, d, J = 8.0Hz), 7.00 (1H, dd, J = 8.0Hz, 2.0Hz), 7.02 (1H, d, J = 2.0Hz), 7.20 (1H, s), 8.74 (1H, s)

Example 87

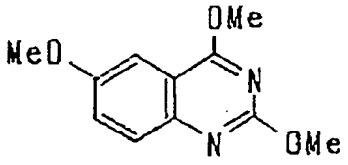
4-(3,4-Methylenedioxybenzyl)oxy-6-methylthioquinazoline



- molecular formula; $C_{17}H_{14}N_2O_3Cl$
- yield(%); 69
- m.p.(°C); 104 ~ 105
- Mass; 327 $(M+H)^+$
- NMR δ ($CDCl_3$);
  2.59 (3H, s), 5.56 (2H, s), 6.00 (2H, s), 6.85 (1H, d, J = 8.0Hz), 7.01 (1H, dd, J = 8.0Hz, 1.6Hz), 7.03 (1H, d, J = 1.6Hz), 7.72 (1H, dd, J = 8.8Hz, 1.6Hz), 7.88 (1H, d, J = 8.8Hz), 7.89 (1H, d, J = 1.6Hz), 8.78 (1H, s)

Example 88

2,4,6-Trimethoxyquinazoline



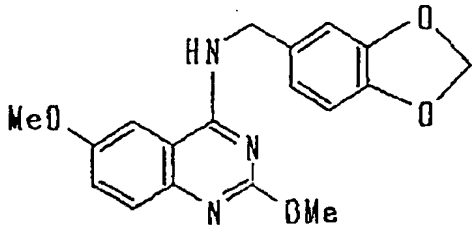
5.0 g (0.022 mol) of 2,4-dichloro-6-methoxyquinazoline was suspended in 150 ml of methanol, followed by the gradual addition of 3.5 g of sodium hydride. The obtained mixture was heated under reflux. After several hours, the reaction mixture was concentrate under a reduced pressure, followed by the addition of water. The crystalline precipitate thus formed was recovered by filtration, washed with water and air-dried to give 4.8 g of the title compound as a crude yellow crystal.

- m.p.; 143 ~ 144
- Mass; 221 $(M+1)_+$
- NMR δ ($CDCl_3$);

  3.90 (3H, s), 4.08 (3H, s), 4.18 (3H, s), 7.36 (1H, d, J=2.8Hz), 7.39 (1H, dd, J=8.8Hz, 2.8Hz), 7.67 (1H, d, J=2.8Hz)

Example 89

2,6-Dimethoxy-4-(3,4-methylenedioxybenzyl)aminoquinazoline



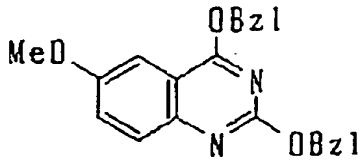
3.75 g (24.8 mmol) of piperonylamine was added to a solution of 2.00 g (8.26 mmol) of the 2,4,6-trimethoxyquinazoline prepared in Example 88 in dimethyl sulfoxide (15 ml). The obtained mixture was stirred under heating at 150 to 160 °C. After one hour, the reaction mixture was purified by silica gel column chromatography (ethyl acetate/n-hexane) and recrystallized from ethyl acetate/n-hexane to give 0.50 g of the title compound as a pale-yellow crystal.

- molecular formula; $C_{18}H_{17}N_3O_4$
- yield(%); 18
- m.p.(°C); 166 ~ 167
- Mass; 340 $(M+1)^+$
- NMR δ ($CDCl_3$);

  3.89 (3H, s), 4.03 (3H, s), 4.77 (2H, d, J=5.2Hz), 5.94 (2H, s), 6.76 (1H, d, J=8.0Hz), 6.89 (1H, dd, J=8.0Hz, 1.2Hz), 6.93 (1H, d, J=1.2Hz), 7.29 (1H, dd, J=8.8Hz, 2.8Hz), 7.32 (1H, brs), 7.59 (1H, d, J=8.8Hz)

Example 90

2,4-Bisbenzyloxy-6-methoxyquinazoline

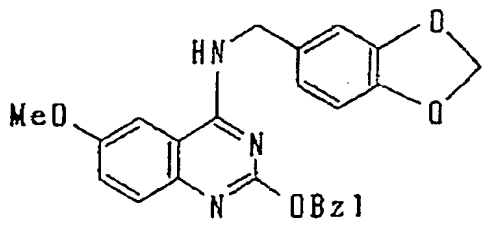


3 ml of benzyl alcohol was dissolved in 50 ml of tetrahydrofuran, followed by the addition of 1.0 g of sodium hydride. The obtained mixture was stirred at 40 to 50 °C for 30 minutes, followed by the addition of 2.50 g (0.0109 mol) of 2,4-dichloro-6-methoxyquinazoline. The obtained mixture was heated under reflux for several hours, followed by the addition of water. The obtained mixture was extracted with chloroform and the organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to remove the solvent. The obtained crystalline residue was recrystallized from chloroform/n-hexane to give 3.84 g of the title compound as a yellow crystal.

- yield(%); 95
- m.p.(°C); 144 ~ 145
- Mass; 373 $(M+1)^+$
- NMR δ ($CDCl_3$);
  3.87 (3H, s), 5.53 (2H, s), 5.62 (2H, s), 7.31 ~ 7.55 (12H, m), 7.70 (1H, d, J=8.8Hz)

Example 91

2-Benzyloxy-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline

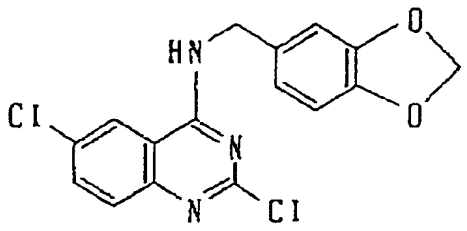


1.25 g (8.27 mmol) of piperonylamine was added to a solution of 1.00 g (2.69 mmol) of the 2,4-bisbenzyloxy-6-methoxyquinazoline prepared in Example 90 in dimethyl sulfoxide (10 ml). The obtained mixture was stirred at 160 to 180 °C. After one hour, the reaction mixture was purified by silica gel column chromatography (ethyl acetate/n-hexane) and recrystallized from ethyl acetate/n-hexane to give 0.20 g of the title compound as a colorless needle.

- molecular formula; $C_{24}H_{21}N_3O_4$
- yield(%); 18
- m.p.(°C); 163 ~ 164
- Mass; 416 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.86 (3H, s), 4.75 (2H, d, J=5.2Hz), 5.49 (2H, s), 5.68 (1H, brs), 5.96 (2H, s), 6.79 (1H, d, J=8.0Hz), 6.84 ~ 6.87 (3H, m), 7.28 ~ 7.36 (4H, m), 7.51 ~ 7.53 (2H, m), 7.63 (1H, d, J=9.2Hz)

Example 92

2,6-Dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline

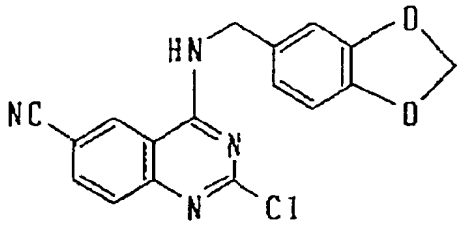


A mixture comprising 3.6 g of 2,4,6-trichloroquinazoline, 2.4 g of piperonylamine, 1.6 g of triethylamine and 50 ml of isopropyl alcohol was heated under reflux for 1.5 hours and hot-filtered to give 5.2 g of the title compound as a filter cake.

- molecular formula; $C_{16}H_{11}N_3O_2Cl_2$
- yield(%); 98
- m.p.(°C); 215
- Mass; 349 $(M+1)^+$
- NMR δ (DMSO-D_6);
  4.61 (2H, s), 5.97 (2H, s), 6.85 (2H, s), 6.95 (1H, s), 7.63 (1H, d, J=8.8Hz), 7.80 (1H, dd, J=8.8Hz, 2.4Hz), 8.45 (1H, d, J=2.4Hz), 9.24 (1H, br)

Example 93

2-Chloro-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline

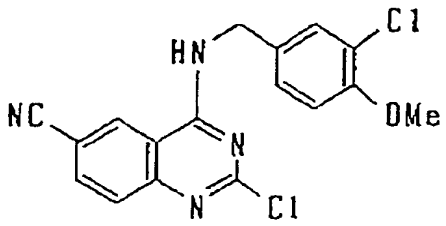


35 ml of isopropyl alcohol, 900 mg of triethylamine and 1.35 g of piperonylamine were added to 2 g of 2,4-dichloro-6-cyanoquinazoline. The obtained mixture was heated under reflux for 1.5 hours and hot-filtered to recover a precipitate. Thus, 2.4 g of the title compound was obtained.

- molecular formula; $C_{17}H_{11}N_4O_2Cl$
- yield(%); 79
- m.p.(°C); 234 ~ 236 (dec.)
- Mass; 339 $(M+1)^+$
- NMR δ (DMSO-d_6);
  4.63 (2H, d, J=5.6Hz), 5.97 (2H, s), 6.86 (2H, s), 6.97 (1H, s), 7.72 (1H, d, J=8.4Hz), 8.10 (1H, dd, J=8.4Hz, 1.8Hz), 8.90 (1H, d, J=1.8Hz), 9.50 (1H, br)

Example 94

2-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline



3.9 g of 3-chloro-4-methoxybenzylamine, 3.97 g of triethylamine and 200 ml of 2-propanol were added to 4 g of 2,4-dichloro-6-cyanoquinazoline. The obtained mixture was refluxed for 30 minutes, cooled to room temperature and filtered to recover a crystalline precipitate. The precipitate was washed with water and chloroform successively to give 5.563 g of the title compound.

- molecular formula; $C_{17}H_{12}N_4OCl_2$
- yield(%); 87
- m.p.(°C); 264 ~ 266
- Mass m/e; 359 (M + 1)
- NMR δ ($CDCl_3$);

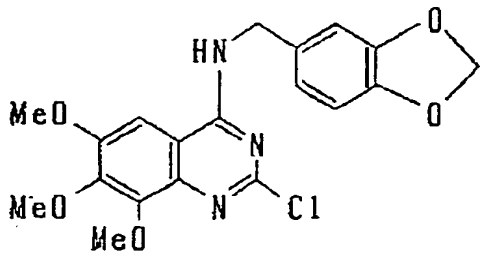
  3.90 (3H, s), 4.73 (2H, d, J = 5.2Hz), 6.92 (1H, d, J = 8.4), 7.33 (1H, dd, J = 8.4Hz, 2.0Hz), 7.45 (1H, d, J = 2.0Hz), 7.74 (1H, d, J = 8.4Hz), 7.83 (1H, dd, J = 8.4Hz, 1.6Hz), 8.78 (1H, d, J = 1.6Hz), 8.85 (1H, brs)

Examples 95 to 105

The following compounds were prepared in a similar manner to those of Examples 88 to 94.

Example 95

2-Chloro-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline

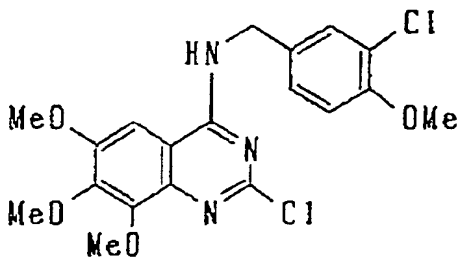


- molecular formula; $C_{19}H_{18}N_3O_5Cl$
- yield(%); 50
- m.p.(°C); 193 ~ 194
- Mass; 404 $(M + H)^+$
- NMR δ ($CDCl_3$);

  3.94 (3H, s), 4.03 (3H, s), 4.10 (3H, s), 4.75 (2H, d, J = 5.2Hz), 5.65 (1H, brs), 5.98 (2H, s), 6.59 (1H, s), 6.81 (1H, d, J = 8.0Hz), 6.89 (1H, d, J = 8.0Hz), 6.91 (1H, s)

Example 96

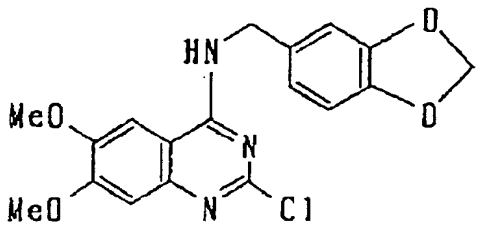
2-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{19}Cl_2N_3O_4$
- yield(%); 45
- m.p.(°C); 199 ~ 200
- Mass; 424 $(M+1)^+$
- NMR δ ($CDCl_3$);
  3.89 (3H, s), 3.95 (3H, s), 4.02 (3H, s), 4.08 (3H, s), 4.76 (2H d, J=5.6Hz), 6.39 (1H, brs), 6.83 (1H, s), 6.89 (1H, d, J=8.3Hz), 7.31 (1H, dd, J=8.4Hz, 2.0Hz), 7.40 (1H, d, J=2.0Hz)

Example 97

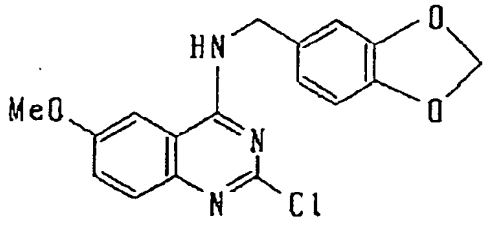
2-Chloro-4-(3,4-methylenedioxybenzyl)amino-6,7-dimethoxyquinazoline



- molecular formula; $C_{18}H_{16}N_3O_4Cl$
- yield(%); 97
- m.p.(°C); 177 ~ 178
- Mass; 374 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.95 (3H, s), 3.97 (3H, s), 4.75 (2H, d, J=5.2Hz), 5.74 (1H, brt, J=5.2Hz), 5.97 (2H, s), 6.80 (1H, d, J=8.0Hz), 6.81 (1H, s), 6.88 (1H, dd, J=8.0Hz, 2.0Hz), 6.91 (1H, d, J=2.0Hz), 7.14 (1H, s)

Example 98

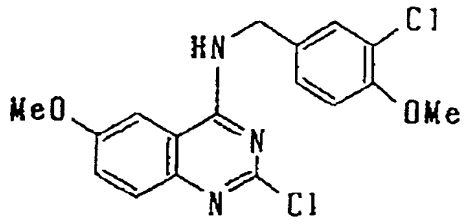
2-Chloro-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



- molecular formula; $C_{17}H_{14}N_3O_3Cl$
- yield(%); 80
- m.p.(°C); 202 ~ 203
- Mass; 344 $(M+1)^+$
- NMR δ ($CDCl_3$);
  3.91 (3H, s), 4.77 (2H, d, J=5.6Hz), 5.94 (2H, s), 6.76 (1H, d, J=8.0Hz), 6.91 (1H, dd, J=8.0Hz, 1.6Hz), 6.95 (1H, d, J=1.6Hz), 7.35 (1H, dd, J=9.2Hz, 2.8Hz), 7.46 (1H, brd, J=2.8Hz), 7.69 (1H, d, J=9.2Hz), 7.90 (1H, brs)

Example 99

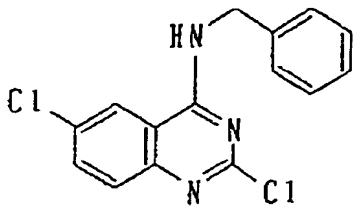
2-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-methoxyquinazoline



- molecular formula; $C_{17}H_{15}N_3O_2Cl_2$
- yield(%); 88
- m.p.(°C); 171 ~ 172
- Mass; 364 $(M+1)^+$
- NMR δ (DMSO);
  3.83 (3H, s), 3.88 (3H, s), 4.68 (2H, d, J=5.6Hz), 7.13 (1H, d, J=8.8Hz), 7.33 (1H, dd, J=2.4Hz, 8.8Hz), 7.44 (1H, dd, J=2.8Hz, 9.2Hz), 7.46 (1H, d, J=2.4Hz), 7.58 (1H, d, J=9.2Hz), 7.72 (1H, d, J=2.8Hz), 9.05 (1H, t, J=5.6Hz)

Example 100

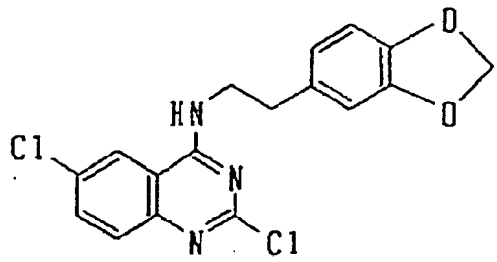
2,6-Dichloro-4-benzylaminoquinazoline



- molecular formula; $C_{15}H_{11}N_3Cl_2$
- yield(%); 77
- m.p.(°C); 227 ~ 228
- NMR δ ($CDCl_3$);
  4.85 (2H, d, J=5.2Hz), 5.97 (1H, brs), 7.33 ~ 7.43 (5H, m), 7.62 (1H, d, J=2.0Hz), 7.68 (1H, dd, J=8.8Hz, 2.0Hz), 7.74 (1H, d, J=8.8Hz)

Example 101

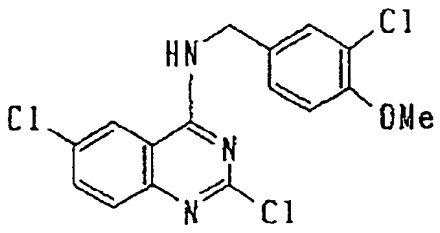
2,6-Dichloro-4-[2-(3,4-methylenedioxyphenyl)ethyl]aminoquinazoline



- molecular formula; $C_{17}H_{13}N_3O_2Cl_2$
- yield(%); 71
- m.p.(°C); 228 ~ 229
- NMR δ (DMSO-d_6);
  2.88 (2H, t, J=7.4Hz), 3.68 (2H, m), 5.96 (2H, s), 6.70 (1H, dd, J=8.0Hz, 1.6Hz), 6.81 (1H, d, J=8.0Hz), 6.87 (1H, d, J=1.6Hz), 7.63 (1H, d, J=8.8Hz), 7.80 (1H, dd, J=8.8Hz, 2.0Hz), 8.40 (1H, d, J=2.0Hz), 8.86 (1H, d, J=5.2Hz)

Example 102

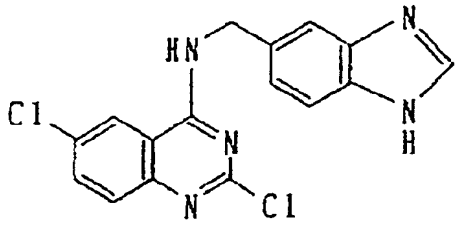
2,6-Dichloro-4-(3-chloro-4-methoxybenzyl)aminoquinazoline



- molecular formula; $C_{16}H_{12}N_3OCl_3$
- yield(%); 93
- m.p.(°C); 207 ~ 208
- Mass m/e; 368 (M + 1)
- NMR δ ($CDCl_3$);
  3.90 (3H, s), 4.73 (2H, d, J = 5.6Hz), 6.91 (1H, d, J = 8.4Hz), 7.32 (1H, d, J = 8.4Hz, 2.0Hz), 7.45 (1H, d, J = 2.0Hz), 7.62 (1H, dd, J = 8.8Hz, 2.0Hz), 7.66 (1H, d, J = 8.8Hz), 8.07 (1H, brs), 8.16 (1H, d, J = 2.0Hz)

Example 103

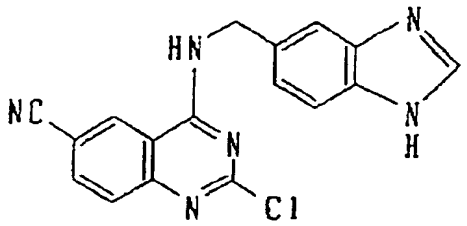
2,6-Dichloro-4-(benzimidazol-5-yl)methylaminoquinazoline



- molecular formula; $C_{16}H_{11}N_5Cl_2$ (344.205)
- yield(%); 81
- m.p.(°C); >290
- Mass; 344 $(M + 1)^+$
- NMR δ (DMSO);
  4.85 (2H, d, J = 6.0Hz), 7.25 (1H, dd, J = 1.6Hz, 6.4Hz), 7.57 (1H, d, J = 6.4Hz), 7.60 (1H, s), 7.66 (1H, d, J = 8.8Hz), 7.83 (1H, dd, J = 2.0Hz, 8.8Hz), 8.21 (1H, s), 8.44 (1H, brs), 8.52 (1H, d, J = 2.0Hz), 9.37 (1H, t, J = 6.0Hz)

Example 104

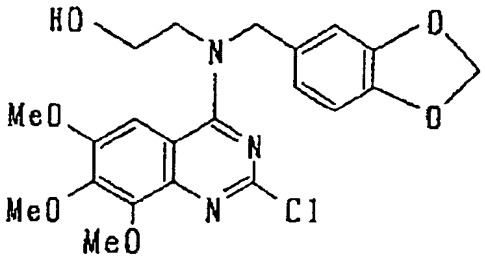
2-Chloro-4-(benzimidazol-5-yl)methylamino-6-cyanoquinazoline



- molecular formula; $C_{17}H_{11}N_6Cl$ (334.5)
- yield(%); 58
- m.p.(°C); >290
- Mass; 335 $(M+1)^+$
- NMR δ (DMSO-d_6);
  4.81 (2H, s), 7.21 ~ 7.68 (3H, m), 7.73 (1H, d, J=8.8Hz), 8.10 (1H, d, J=8.8Hz), 8.17 (1H, s), 8.91 (1H, s), 9.55 (1H, br)

Example 105

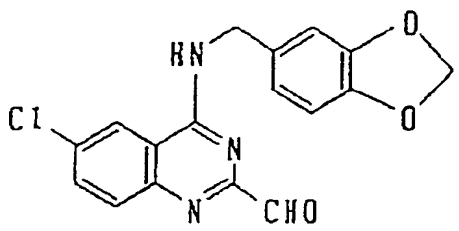
2-Chloro-4-[N-(2-hydroxyethyl)-(3,4-methylenedioxybenzyl)amino]-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{22}N_3O_6Cl$
- yield(%); 55
- Mass; 448 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.38 (3H, s), 3.88 (2H, t J=4.4Hz), 4.01 (2H, t, J=4.4Hz), 4.03 (3H, s), 4.07 (3H, s), 4.92 (2H, s), 6.01 (2H, s), 6.88 ~ 6.91 (3H, m), 7.00 (1H, s)

Example 106

2-Formyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

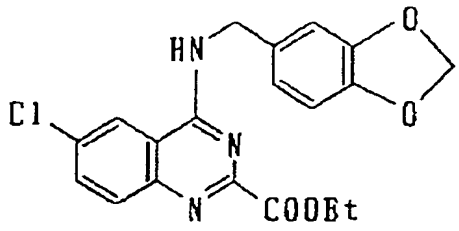


0.50 g (0.0013 mol) of 2-ethoxycarbonyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline was dissolved in a solvent mixture comprising 20 ml of methylene chloride and 20 ml of tetrahydrofuran. 2.6 ml of a 1.0 M solution of diisobutylaluminum hydride in toluene was dropped into the solution prepared above at -78 °C under stirring. The obtained mixture was stirred at -78 °C for several hours, followed by the addition of 20 ml of methanol. The obtained mixture was distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography and recrystallized from ethyl acetate/n-hexane to give 0.23 g of the title compound as a pale-yellow crystal.

- yield(%); 52
- m.p.(°C); 200 ~ 202 (dec.)
- Mass; 342 $(M+1)^+$
- NMR δ ($CDCl_3$);
  4.86 (2H, d, J = 5.2Hz), 5.98 (2H, s), 6.81 (1H, d, J = 7.6Hz), 6.90 (1H, d, J = 7.6Hz), 6.92 (1H, s), 7.72 (1H, d, J = 2.0Hz), 7.77 (1H, dd, J = 8.8Hz, 2.0Hz), 8.01 (1H, d, J = 8.8Hz), 10.05 (1H, s)

Example 107

2-Ethoxycarbonyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



2.72 g (0.0100 mol) of 2-ethoxycarbonyl-4,6-dichloroquinazoline, 1.75 g (0.0116 mol) of piperonylamine and 1.60 g (0.0151 mol) of sodium carbonate were mixed with 100 ml of isopropyl alcohol. The obtained mixture was heated under reflux for 24 hours and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography and recrystallized from chloroform/n-hexane to give 3.56 g of the title compound as a colorless needle.

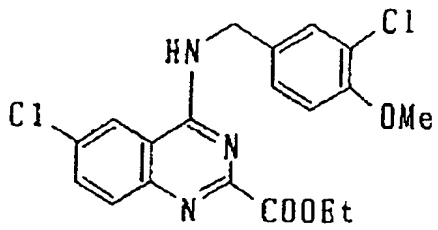
- molecular formula; $C_{19}H_{16}N_3O_4Cl$
- yield(%); 92
- m.p.(°C); 212 ~ 213
- Mass; 386 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.49 (3H, t, J = 7.2Hz), 1.54 (2H, q, J = 7.2Hz), 4.83 (2H, d, J = 5.6Hz), 5.96 (1H, brs), 5.97 (2H, s), 6.80 (1H, d, J = 8.0Hz), 6.91 (1H, dd, J = 8.0Hz, 1.6Hz), 6.97 (1H, d, J = 1.6Hz), 7.70 (1H, d, J = 2.0Hz), 7.72 (1H, dd, J = 8.8Hz, 2.0Hz), 8.00 (1H, d, J = 8.8Hz)

Examples 108 to 111

The following compounds were prepared in a similar manner to that of Examples 106 or 107.

Example 108

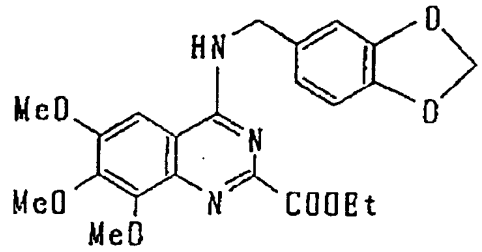
2-Ethoxycarbonyl-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{19}H_{17}N_3O_3Cl_2$
- yield(%); 88
- m.p.(°C); 185 ~ 186
- Mass; 406 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.49 (3H, t, J=7.2Hz), 3.90 (3H, s), 4.54 (2H, q, J=7.2Hz), 4.84 (2H, d, J=5.2Hz), 6.09 (1H, brs), 6.90 (1H, d, J=8.4Hz), 7.33 (1H, dd, J=8.4Hz, 2.4Hz), 7.48 (1H, d, J=2.4Hz), 7.72 (1H, dd, J=8.8Hz, 2.4Hz), 7.74 (1H, d, J=2.4Hz), 7.99 (1H, d, J=8.8Hz)

Example 109

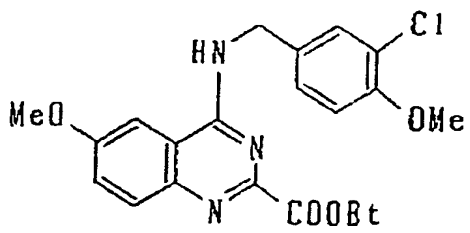
2-Ethoxycarbonyl-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{22}H_{23}N_3O_7$
- yield(%); quantitative
- m.p.(°C); 163 ~ 165 (dec.)
- Mass; 442 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.45 (3H, t, J=7.2Hz), 3.94 (3H, s), 4.02 (3H, s), 4.18 (3H, s), 4.46 (2H, q, J=7.2Hz), 4.80 (2H, d, J=5.2Hz), 5.89 (1H, brt, J=5.2Hz), 5.94 (2H, s), 6.74 (1H, d, J=7.6Hz), 6.76 (1H, s), 6.86 (1H, dd, J=7.6Hz, 1.6Hz), 6.94 (1H, d, J=1.6Hz)

Example 110

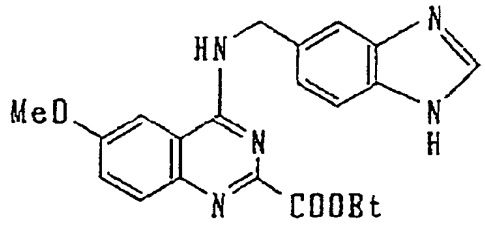
2-Ethoxycarbonyl-4-(3-chloro-4-methoxybenzyl)amino-6-methoxyquninazoline



- molecular formula; $C_{20}H_{20}N_3O_4Cl$
- yield(%); 73
- m.p.(°C); 192 ~ 193
- Mass; 402 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.49 (3H, t, J=7.2Hz), 3.90 (3H, s), 3.91 (3H, s), 4.53 (2H, q, J=7.2Hz), 4.86 (2H, d, J=5.6Hz), 5.90 (1H, brt, J=5.6Hz), 6.90 (1H, d, J=8.4Hz), 6.96 (1H, d, J=2.4Hz), 7.36 (1H, dd, J=8.4Hz, 2.4Hz), 7.44 (1H, dd, J=9.2Hz, 2.4Hz), 7.49 (1H, d, J=2.4Hz), 8.00 (1H, d, J=9.2Hz)

Example 111

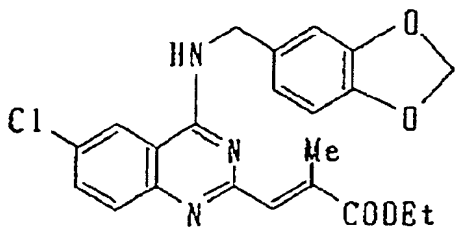
2-Ethoxycarbonyl-4-(benzimidazol-5-ylmethyl)amino-6-methoxyquinazoline



- molecular formula; $C_{20}H_{19}N_5O_3$
- yield(%); 48
- m.p.(°C); 244 ~ 245 (dec.)
- Mass; 378 $(M+1)^+$
- NMR δ (DMSO-d_6);
  1.35 (3H, t, J=7.2Hz), 3.90 (3H, s), 4.33 (2H, q, J=7.2Hz), 4.94 (2H, d, J=6.0Hz), 7.31 (1H, d, J=8.0Hz), 7.47 (1H, dd, J=8.8Hz, 2.8Hz), 7.53 (1H, d, J=8.0Hz), 7.65 (1H, brs), 7.77 (1H, d, J=8.8Hz), 7.78 (1H, s), 8.17 (1H, s), 8.89 (1H, brt, J=6.0Hz)

Example 112

(E)-2-(2-Ethoxycarbonyl-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



0.52 g (0.013 mol) of sodium hydride was added to a solution of 4.00 g (0.0117 mol) of 2-formyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline in 250 ml of tetrahydrofuran. 2.8 ml (0.013 mol) of triethyl 2-phosphonopropionate was dropped into the mixture prepared above under stirring and cooling with ice. The mixture thus prepared was stirred under cooling with ice for a while, heated to room temperature and stirred for additional one hour, followed by the addition of 1.5 ml of 8M hydrochloric acid/ethanol. The obtained mixture was passed through a small amount of silica gel and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) and recrystallized from chloroform/n-hexane to give 2.00 g of the title compound.

- molecular formula; $C_{22}H_{20}N_3O_4Cl$
- yield(%); 40
- m.p.(°C); 179 ~ 180 (dec.)
- Mass; 426 $(M+1)^+$
- NMR δ ($CDCl_3$);

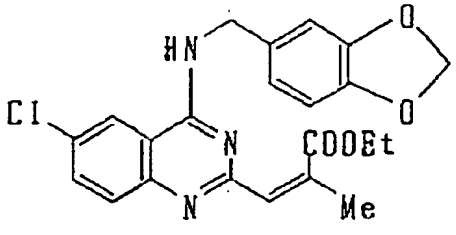
  1.35 (3H, t, J = 7.2Hz), 2.50 (3H, d, J = 1.6Hz), 4.29 (2H, q, J = 7.2Hz), 4.78 (2H, d, J = 5.2Hz), 5.77 (1H, brt, J = 5.2Hz), 5.97 (2H, s), 6.81 (1H, d, J = 8.0Hz), 6.87 (1H, dd, J = 8.0Hz, 1.6Hz), 6.89 (1H, d, J = 1.6Hz), 7.62 (1H, q, J = 1.6Hz), 7.64 (1H, d, J = 2.0Hz), 7.68 (1H, dd, J = 8.8Hz, 2.0Hz), 7.81 (1H, d, J = 8.8Hz)

Examples 113 to 119

The following compounds were prepared in a similar manner to that of Example 112.

Example 113

(Z)-2-(2-Ethoxycarbonyl-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

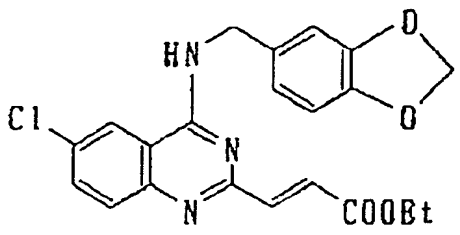


- molecular formula; $C_{22}H_{20}N_3O_4Cl$
- yield(%); 13
- amt. of product(g); 0.64
- m.p.(°C); 162 ~ 164 (dec.)
- Mass; 426 $(M+1)^+$

- NMR δ ($CDCl_3$);
  1.20 (3H, t, J = 7.2Hz), 2.17 (3H, d, J = 1.6Hz), 4.21 (2H, q, J = 7.2Hz), 4.70 (2H, d, J = 4.8Hz), 5.64 (1H, brs), 5.97 (2H, s), 6.53 (1H, q, J = 1.6Hz), 6.81 (1H, d, J = 7.6Hz), 6.85 (1H, dd, J = 7.6Hz, 1.6Hz), 6.87 (1H, d, J = 1.6Hz), 7.58 (1H, d, J = 2.4Hz), 7.62 (1H, dd, J = 8.8Hz, 2.4Hz), 7.71 (1H, d, J = 8.8Hz)

Example 113

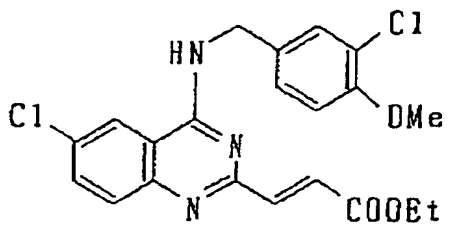
(E)-2-(2-Ethoxycarbonylvinyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{18}N_3O_4Cl$
- yield(%); 67
- m.p.(°C); 195 ~ 196
- Mass; 412 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.35 (3H, t, J = 7.2Hz), 4.29 (2H, q, J = 7.2Hz), 4.80 (2H, d, J = 5.2Hz), 5.77 (1H, brs), 5.97 (2H, s), 6.81 (1H, d, J = 7.6Hz), 6.89 (1H, d, J = 7.6Hz), 6.90 (1H, s), 7.21 (1H, d, J = 15.6Hz), 7.64 (1H, d, J = 2.0Hz), 7.66 (1H, d, J = 15.6Hz), 7.68 (1H, dd, J = 9.2Hz, 2.0Hz), 7.82 (1H, d, J = 9.2Hz)

Example 115

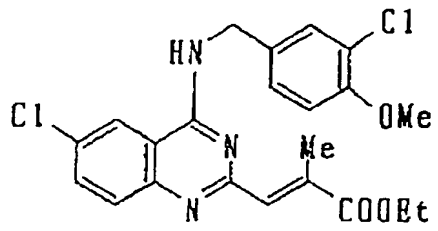
(E)-2-(2-Ethoxycarbonylvinyl)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{19}N_3O_4Cl_2$
- yield(%); 74
- m.p.(°C); 211 ~ 212
- Mass; 432 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.35 (3H, t, J = 7.2Hz), 3.89 (3H, s), 4.28 (2H, q, J = 7.2Hz), 4.79 (2H, d, J = 5.6Hz), 6.91 (1H, d, J = 8.4Hz), 7.16 (1H, d, J = 15.6Hz), 7.33 (1H, dd, J = 8.4Hz, 2.0Hz), 7.46 (1H, d, J = 2.0Hz), 7.62 (1H, d, J = 15.6Hz), 7.64 (1H, dd, J = 8.8Hz, 2.4Hz), 7.75 (1H, d, J = 8.8Hz), 7.77 (1H, brs), 8.16 (1H, d, J = 2.4Hz)

Example 116

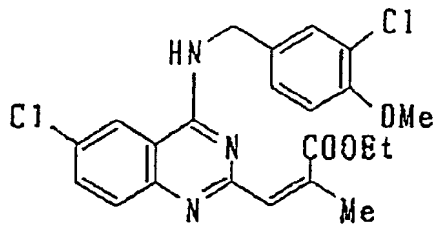
(E)-2-(2-Ethoxycarbonyl-1-propenyl)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{22}H_{21}N_3O_3Cl_2$
- yield(%); 54
- m.p.(°C); 154 ~ 155
- Mass; 446 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.35 (3H, t, J=7.2Hz), 2.48 (3H, d, J=1.6Hz), 3.91 (3H, s), 4.29 (2H, q, J=7.2Hz), 4.80 (2H, d, J=5.2Hz), 5.82 (1H, brt, J=5.2Hz), 6.92 (1H, d, J=8.8Hz), 7.27 (1H, dd, J=8.8Hz, 2.0Hz), 7.42 (1H, d, J=2.0Hz), 7.62 (1H, q, J=1.6Hz), 7.67 (1H, d, J=2.4Hz), 7.69 (1H, dd, J=8.8Hz, 2.4Hz), 7.82 (1H, d, J=8.8Hz)

Example 117

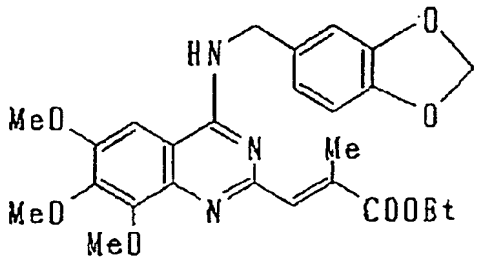
(Z)-2-(2-Ethoxycarbonyl-1-propenyl)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{22}H_{21}N_3O_4Cl_2$
- yield(%); 11
- m.p.(°C); 141 ~ 142
- Mass; 446 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.19 (3H, t, J=7.2Hz), 2.17 (3H, d, J=1.6Hz), 3.91 (3H, s), 4.19 (2H, q, J=7.2Hz), 4.73 (2H, d, J=5.2Hz), 5.69 (1H, brt, J=5.2Hz), 6.53 (1H, q, J=1.6Hz), 6.92 (1H, d, J=8.4Hz), 7.26 (1H, dd, J=8.4Hz, 2.0Hz), 7.40 (1H, d, J=2.0Hz), 7.60 (1H, d, J=2.0Hz), 7.63 (1H, dd, J=8.8Hz, 2.0Hz), 7.71 (1H, d, J=8.8Hz)

Example 118

(E)-2-(2-Ethoxycarbonyl-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6,7,8-tribethoxyquinazoline

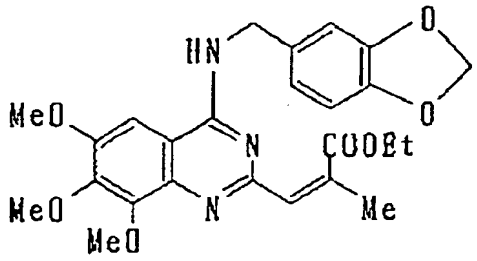


- molecular formula; $C_{25}H_{27}N_3O_7$
- yield(%); 51
- m.p.(°C); 175 ~ 176
- Mass; 482 $(M+1)^+$
- NMR δ ($CDCl_3$);

  1.35 (3H, t, J=7.2Hz), 2.52 (3H, d, J=1.6Hz), 3.95 (3H, s), 4.04 (3H, s), 4.14 (3H, s), 4.28 (2H, q, J=7.2Hz), 4.80 (2H, d, J=5.2Hz), 5.60 (1H, brt, J=5.2Hz), 5.96 (2H, s), 6.67 (1H, s), 6.80 (1H, d, J=8.0Hz), 6.87 (1H, dd, J=8.0Hz, 1.6Hz), 6.90 (1H, d, J=1.6Hz), 7.69 (1H, q, J=1.6Hz)

Example 119

(Z)-2-(2-Ethoxycarbonyl-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethyoxquinazoline

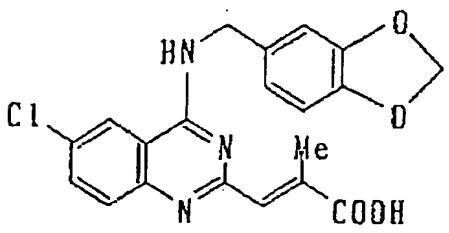


- molecular formula; $C_{25}H_{27}N_3O_7$
- yield(%); 11
- m.p.(°C); 157 ~ 158 (dec.)
- Mass; 482 $(M+1)^+$
- NMR δ ($CDCl_3$);

  1.19 (3H, t, J=7.2Hz), 2.16 (3H, s), 3.92 (3H, s), 4.02 (3H, s), 4.09 (3H, s), 4.21 (2H, q, J=7.2Hz), 4.72 (2H, d, J=5.2Hz), 5.43 (1H, brs), 5.96 (2H, s), 6.59 ~ 6.61 (2H, m), 6.80 (1H, d, J=8.0Hz), 6.86 ~ 6.89 (2H, m)

Example 120

(E)-2-(2-Carboxy-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



1.00 g (0.0023 mol) of (E)-2-(2-ethoxycarbonylpropenyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline was dissolved in a mixture comprising 5 ml of tetrahydrofuran and 20 ml of ethanol, followed by the addition of 20 ml of a 1N aqueous solution of sodium hydroxide. The obtained mixture was stirred at room temperature for several hours, neutralized with 20 ml of 1N hydrochloric acid and concentrated under a reduced pressure. The crystal thus formed was recovered by filtration, washed with water and air-dried to give 0.85 g of the title compound.

- molecular formula; $C_{20}H_{16}N_3O_4Cl$
- yield(%); 91
- m.p.(°C); 145 ~ 146
- Mass; 398 $(M+1)^+$
- NMR δ (DMSO-d_6);

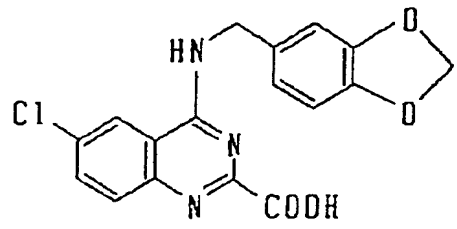
  2.36 (3H, d, J = 1.6Hz), 4.70 (2H, d, J = 5.6Hz), 5.97 (2H, s), 6.85 (2H, s), 6.95 (1H, s), 7.34 (1H, q, J = 1.6Hz), 7.72 (1H, d, J = 8.8Hz), 7.79 (1H, dd, J = 8.8Hz, 2.0Hz), 8.46 (1H, d, J = 2.0Hz), 8.86 (1H, brt, J = 5.6Hz)

Examples 121 to 128

The following compounds were prepared in a similar manner to that of Example 120.

Example 121

2-Carboxy-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

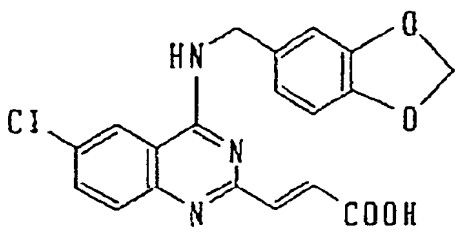


- molecular formula; $C_{17}H_{12}N_3O_4Cl$
- yield(%); quantitative
- m.p.(°C); 240 (dec.)
- Mass; 402 $(M-1+2Na)^+$
- NMR δ (DMSO-d_6);

  4.71 (2H, d, J = 5.6Hz), 5.96 (2H, s), 6.83 (1H, d, J = 8.0Hz), 6.89 (1H, dd, J = 8.0Hz, 1.2Hz), 7.06 (1H, d, J = 1.2Hz), 7.75 (1H, dd, J = 8.8Hz, 2.4Hz), 7.90 (1H, d, J = 8.8Hz), 8.48 (1H, d, J = 2.4Hz), 8.82 (1H, brt, J = 5.6Hz)

Example 122

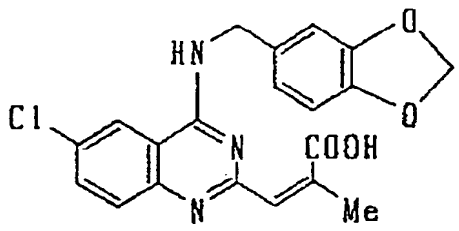
(E)-2-(2-Carboxyvinyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{19}H_{14}N_3O_4Cl$
- yield(%); 43
- m.p.(°C); 114 ~ 115
- Mass; 428 $(M-1+2Na)^+$
- NMR δ (DMSO-d_6);
  4.71 (2H, d, J=5.6Hz), 5.96 (2H, s), 6.84 (1H, d, J=8.0Hz), 6.90 (1H, dd, J=8.0Hz, 1.6Hz), 6.99 (1H, d, J=1.6Hz), 7.02 (1H, d, J=15.6Hz), 7.23 (1H, d, J=15.6Hz), 7.73 (1H, d, J=9.2Hz), 7.78 (1H, dd, J=9.2Hz, 2.0Hz), 8.44 (1H, d, J=2.0Hz), 8.89 (1H, brt, J=5.6Hz)

Example 123

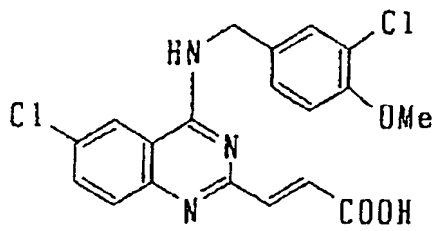
(Z)-2-(2-carboxy-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{16}N_3O_4Cl$
- yield(%); quantitative
- m.p.(°C); 195 ~ 196
- Mass; 398 $(M+1)^+$
- NMR δ (DMSO-d_6);
  2.10 (3H, d, J=1.6Hz), 4.70 (2H, d, J=5.6Hz), 5.97 (2H, s), 6.56 (1H, d, J=1.6Hz), 6.86 (1H, d, J=8.0Hz), 6.91 (1H, dd, J=8.0Hz, 1.6Hz), 7.00 (1H, d, J=1.6Hz), 7.65 (1H, d, J=9.2Hz), 7.81 (1H, dd, J=9.2Hz, 2.4Hz), 8.46 (1H, d, J=2.4Hz), 8.96 (1H, brt, J=5.6Hz)

Example 124

(E)-2-(2-Carboxyvinyl)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline

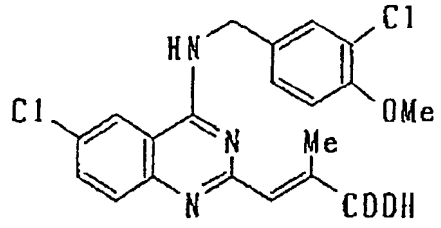


- molecular formula; $C_{19}H_{15}N_3O_3Cl_2$
- yield(%); quantitative
- m.p.(°C); 109 ~ 110
- Mass; 448 $(M-1+2Na)^+$
- NMR δ (DMSO-d_6);

  3.81 (3H, s), 4.73 (2H, d, J = 5.6Hz), 6.95 (1H, d, J = 15.6Hz), 7.05 (1H, d, J = 15.6Hz), 7.08 (1H, d, J = 8.4Hz), 7.37 (1H, dd, J = 8.4Hz, 2.0Hz), 7.48 (1H, d, J = 2.0Hz), 7.68 (1H, d, J = 8.8Hz), 7.73 (1H, dd, J = 8.8Hz, 2.0Hz), 8.42 (1H, d, J = 2.0Hz), 8.91 (1H, brt, J = 5.6Hz)

Example 125

(E)-2-(2-Carboxy-1-propenyl)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline

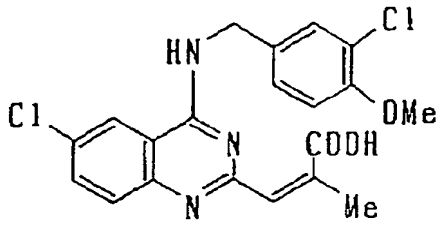


- molecular formula; $C_{20}H_{17}N_3O_3Cl_2$
- yield(%); quantitative
- m.p.(°C); 151 ~ 152
- Mass; 462 (M-1 + 2Na)
- NMR δ (DMSO-d_6);

  2.33 (3H, d, J = 1.2Hz), 3.82 (3H, s), 4.72 (2H, d, J = 5.6Hz), 7.09 (1H, d, J = 8.4Hz), 7.20 (1H, d, J = 1.2Hz), 7.32 (1H, dd, J = 8.4Hz, 2.0Hz), 7.44 (1H, d, J = 2.0Hz), 7.67 (1H, d, J = 8.8Hz), 7.74 (1H, dd, J = 8.8Hz, 2.4Hz), 8.43 (1H, d, J = 2.4Hz), 8.87 (1H, brt, J = 5.6Hz)

Example 126

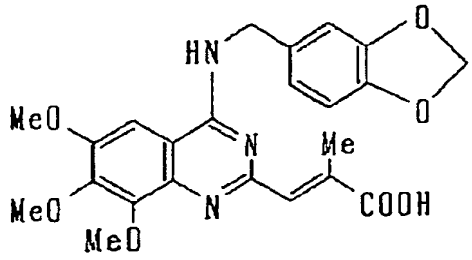
(Z)-2-(2-Carboxy-1-propenyl)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{17}N_3O_3Cl_2$
- yield(%); quantitative
- m.p.(°C); 207 ~ 208 (dec.)
- Mass; 418 $(M+1)^+$
- NMR δ (DMSO-d_6);
  2.10 (3H, d, J=1.4Hz), 3.83 (3H, s), 4.72 (2H, d, J=5.2Hz), 6.54 (1H, d, J=1.4Hz), 7.10 (1H, d, J=8.4Hz), 7.38 (1H, dd, J=8.4Hz, 2.4Hz), 7.49 (1H, d, J=2.4Hz), 7.65 (1H, d, J=8.8Hz), 7.81 (1H, dd, J=8.8Hz, 2.4Hz), 8.44 (1H, d, J=2.4Hz), 8.95 (1H, brt, J=5.2Hz)

Example 127

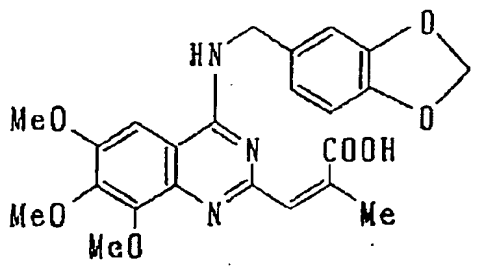
(E)-2-(2-Carboxy-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{23}H_{23}N_3O_7$
- yield(%); 91
- m.p.(°C); 200 ~ 201 (dec.)
- Mass; 454 $(M+1)^+$
- NMR δ (DMSO-d_6);
  2.38 (3H, s), 3.89 (3H, s), 3.92 (3H, s), 4.01 (3H, s), 4.71 (2H, d, J=5.6Hz), 5.97 (2H, s), 6.85 (2H, s), 6.93 (1H, s), 7.37 (1H, s), 7.53 (1H, s), 8.53 (2H, brt, J=5.6Hz), 12.55 (1H, brs)

Example 128

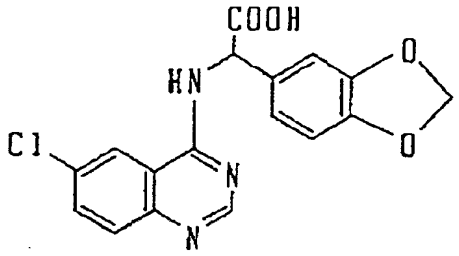
(Z)-2-(2-Carboxy-1-propenyl)-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{23}H_{23}N_3O_7$
- yield(%); 90
- m.p.(°C); 237 ~ 238 (dec.)
- Mass; 454 $(M+1)^+$
- NMR δ (DMSO-d_6);
  2.11 (3H, d, J=1.2Hz), 3.92 ((3H, s), 3.93 (3H, s), 3.94 (3H, s), 4.76 (2H, d, J=5.6Hz), 5.98 (2H, s), 6.8 ~ 6.9 (3H, m), 6.97 (1H, s), 7.61 (1H, s), 9.08 (1H, brt, J=5.6Hz)

Example 129

4-(α-Carboxy-3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



10 ml of ethanol, 5 ml of water and 20 mg of sodium hydroxide were added to 100 mg of 4-(α-ethoxycarbonyl-3,4-methylenedioxybenzyl)amino-6-chloroquinazoline. The obtained mixture was refluxed for 10 minutes and concentrated under a reduced pressure, followed by the addition of 20 ml of water. The obtained mixture was neutralized with 1N hydrochloric acid. The crystal thus precipitated was recovered by filtration. Thus, 45 mg of the title compound was obtained.

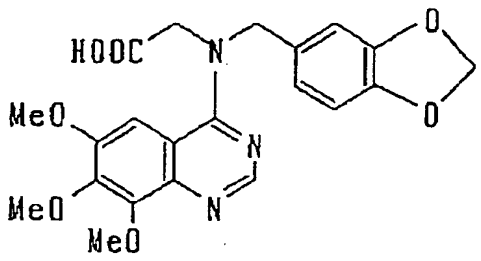
- molecular formula; $C_{17}H_{12}N_3O_4Cl$
- yield(%); 49
- m.p.(°C); 235 ~ 236
- Mass m/e; 358 (M+1)
- NMR δ (DMSO-d_6);
  5.75 (1H, d, J=6.4Hz), 6.01 (2H, s), 6.89 (1H, d, J=8.0Hz), 7.00 (1H, d, J=8.0Hz), 7.08 (1H, s), 7.70 (1H, d, J=8.8Hz), 7.75 (1H, dd, J=1.6Hz, 8.8Hz), 8.49 (1H, s), 8.59 (1H, d, J=6.4Hz), 8.70 (1H, d, J=1.6Hz)

Examples 130 to 131

The following compounds were prepared in a similar manner to that of Example 129.

Example 130

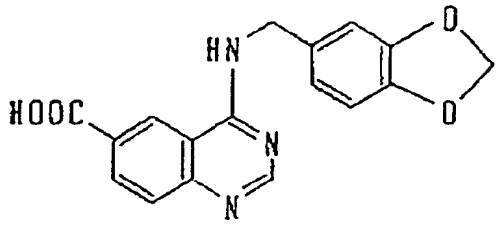
4-[N-(Carboxymethyl)-(3,4-methylenedioxybenzyl)amino]-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{21}N_3O_7$
- yield(%); 90
- m.p.(°C); 134 ~ 136
- Mass; 428 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.43 (3H, s), 4.06 (3H, s), 4.17 (3H, s), 4.62 (2H, s), 5.16 (2H, s), 6.03 (2H, s), 6.87 (1H, s), 6.91 (2H, s), 7.06 (1H, s), 8.87 (1H, s)

Example 131

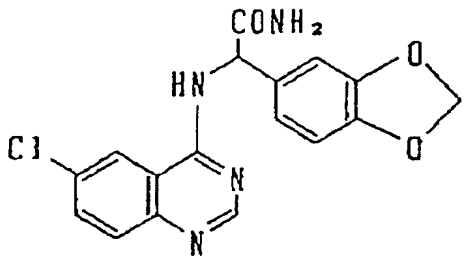
4-(3,4-Methylenedioxybenzyl)amino-6-carboxyquinazoline



- molecular formula; $C_{17}H_{13}N_3O_4$
- yield(%); 98
- m.p.(°C); 247 ~ 248 (dec.)
- Mass; 324 $(M+H)^+$
- NMR δ (DMSO-d_6);
  4.86 (2H, d, J=5.6Hz), 5.99 (2H, s), 6.89 (1H, d, J=8.0Hz), 6.92 (1H, d, J=8.0Hz), 7.02 (1H, s), 7.92 (1H, d, J=8.8Hz), 8.46 (1H, d, J=8.8Hz), 8.96 (1H, s), 9.20 (1H, s), 10.88 (1H, brs)

Example 132

4-(α-Carbamoyl-3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



20 ml of a 10 % solution of ammonia in ethanol was added to 200 mg of 4-(α-ethoxycarbonyl-3,4-methylenedioxybenzyl)amino-6-chloroquinazoline. The obtained mixture was stirred at room temperature for 3 days. The crystal thus precipitated was recovered by filtration. Thus, 60 mg of the title compound was obtained.

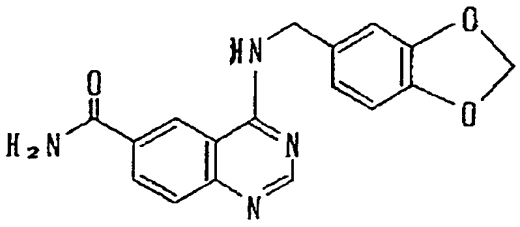
- molecular formula; $C_{17}H_{13}N_4O_3Cl$
- yield(%); 32
- m.p.(°C); 230 ~ 231
- Mass m/e; 357 (M+1)
- NMR δ ($CDCl_3$ + DMSO-d_6);
  5.96 (3H, m), 6.42 (1H, brs), 6.79 (1H, d, J=8.0Hz), 7.09 (1H, dd, J=8.0Hz, 1.6Hz), 7.14 (1H, d, J=1.6Hz), 7.15 (1H, brs), 7.67 (1H, dd, J=8.8Hz, 2.0Hz), 7.75 (1H, d, J=8.8Hz), 8.28 (1H, d, J=2.0Hz), 8.57 (1H, s)

Examples 133 and 134

The following compounds were prepared in a similar manner to that of Example 132.

Example 133

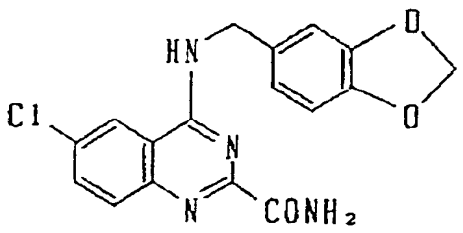
4-(3,4-Methylenedioxybenzyl)amino-6-carbamoylquinazoline



- molecular formula; $C_{17}H_{14}N_4O_3$
- Mass; 323 $(M+H)^+$
- NMR δ (DMSO-d_6);
  4.68 (2H, d, J=6.0Hz), 5.97 (2H, s), 6.85 (1H, d, J=8.0Hz), 6.88 (1H, d, J=8.0Hz), 6.97 (1H, s), 7.55 (1H, brs), 7.70 (1H, d, J=8.4Hz), 7.97 (1H, brs), 8.18 (1H, dd, J=8.4Hz, 1.6Hz), 8.50 (1H, s), 8.84 (1H, d, J=1.6Hz), 8.92 (1H, brt, J=6.0Hz)

Example 134

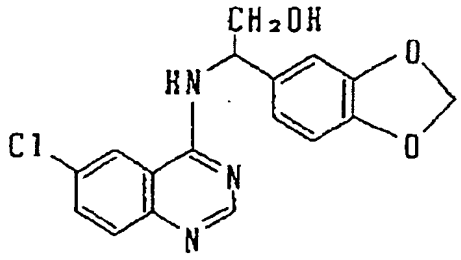
2-Carbamoyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{17}H_{13}ClN_4O_3$
- yield(%); 71
- m.p.(°C); 245 ~ 247 (dec.)
- Mass; 357 (M + 1)
- NMR δ (DMSO-d_6);
  4.77 (2H, d, J = 5.2Hz), 5.97 (2H, s), 6.85 (1H, d, J = 8.0Hz), 6.92 (1H, d, J = 8.0Hz), 7.04 (1H, s), 7.66 (1H, brs), 7.83 (2H, m), 8.07 (1H, brs), 8.49 (1H, s), 8.99 (1H, brs)

Example 135

4-(α-Hydroxymethyl-3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

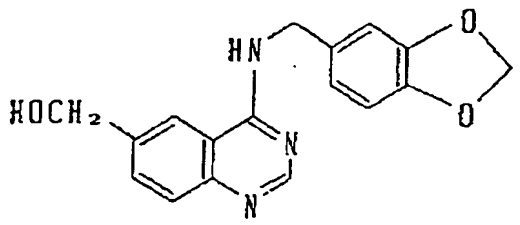


10 ml of ethanol and 197 mg of sodium borohydride were added to 200 mg of 4-(α-ethoxycarbonyl-3,4-methylenedioxybenzyl)amino-6-chloroquinazoline. The obtained mixture was refluxed for 30 minutes, followed by the addition of 5 ml of water. The obtained mixture was concentrated under a reduced pressure, followed by the addition of 10 ml of water. The crystal thus precipitated was recovered by filtration. Thus, 30 mg of the title compound was obtained.

- molecular formula; $C_{17}H_{14}N_3O_3Cl$
- yield(%); 17
- m.p.(°C); 204 ~ 205
- Mass m/e; 344 (M + 1)
- NMR δ ($CDCl_3$ (+ DMSO-d_6));
  3.95 (2H, m), 5.43 (1H, q, J = 4.4Hz), 5.92 (1H, d, J = 1.6Hz), 5.93 (1H, d, J = 1.6Hz), 6.76 (1H, d, J = 8.0Hz), 6.90 (1H, dd, J = 8.0Hz, 1.6Hz), 6.95 (1H, d, J = 1.6Hz), 7.60 (1H, brs), 7.65 (1H, dd, J = 8.4Hz, 2.4Hz), 7.74 (1H, d, J = 8.4Hz), 8.31 (1H, d, J = 2.4Hz), 8.53 (1H, s)

Example 136

4-[(3,4-Methylenedioxybenzyl)amino-6-hydroxymethylquinazoline



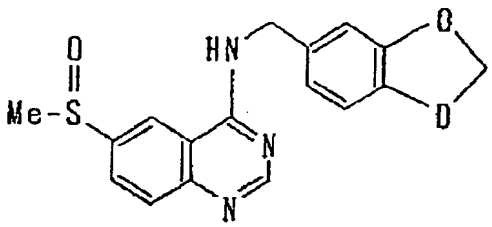
The title compound was prepared in a similar manner to that of Example 135.

- molecular formula; $C_{17}H_{15}N_3O_3$
- yield(%); 34
- m.p.(°C); 176 ~ 177
- Mass m/e; 310 (M+1)
- NMR δ (DMSO-d_6);

  4.62 (2H, d, J=5.6Hz), 4.65 (2H, d, J=5.6Hz), 5.36 (1H, t, J=5.6Hz), 5.94 (2H, s), 6.82 (1H, s), 6.82 (1H, s), 6.92 (1H, s), 7.63 (1H, d, J=8.4Hz), 7.70 (1H, d, J=8.4Hz), 8.20 (1H, s), 8.41 (1H, s), 8.74 (1H, t, J=5.6Hz)

Example 137

4-(3,4-Methylenedioxybenzyl)amino-6-methylsulfinylquinazoline



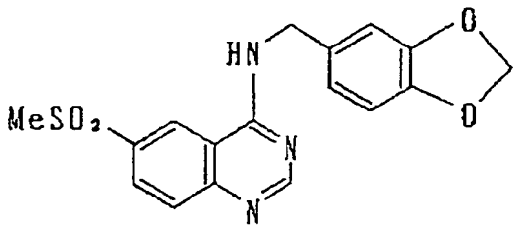
A solution of 1.20 g (6.95 mmol) of m-chloroperbenzoic acid in 30 ml of chloroform was dropped into a solution of 1.80 g (5.53 mmol) of 4-(3,4-methylenedioxybenzyl)amino-6-methylthioquinazoline in 100 ml of chloroform under cooling with ice and stirring. The obtained mixture was stirred under cooling with ice for several hours, washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous magnesium sulfate and filtered. The filtrate was purified by silica gel column chromatography (ethyl acetate/acetone) and recrystallized from chloroform/n-hexane to give 1.51 g of the title compound as a pale-yellow crystal.

- molecular formula; $C_{17}H_{15}N_3O_3S$
- yield(%); 80
- m.p.(°C); 154 ~ 155
- Mass; 342 $(M+H)^+$
- NMR δ ($CDCl_3$);

  2.75 (3H, s), 4.80 (2H, d, J=5.2Hz), 5.96 (2H, s), 6.80 (1H, d, J=8.0Hz), 6.89 (1H, d, J=8.0Hz), 6.91 (1H, s), 7.06 (1H, brs), 7.64 (1H, d, J=8.8Hz), 7.98 (1H, d, J=8.8Hz), 8.43 (1H, s), 8.74 (1H, s)

Example 138

4-(3,4-Methylenedioxybenzyl)amino-6-methylsulfonylquinazoline

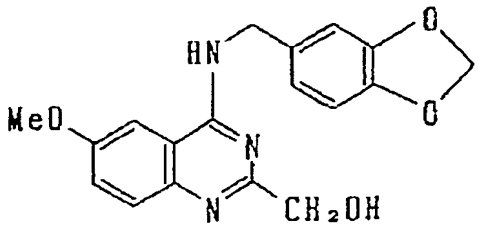


A solution of 0.65 g (3.8 mmol) of m-chloroperbenzoic acid in 20 ml of chloroform was dropped into a solution of 1.00 g (2.93 mmol) of the 4-(3,4-methylenedioxybenzyl)amino-6-methylsulfinylquinazoline prepared in Example 137 under stirring at room temperature. The obtained mixture was stirred at room temperature for several hours, washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous magnesium sulfate and filtered. The filtrate was purified by silica gel column chromatography (ethyl acetate) and recrystallized from chloroform/n-hexane to give 0.85 g of the title compound as a yellow crystal.

- molecular formula; $C_{17}H_{15}N_3O_4S$
- yield(%); 81
- m.p.(°C); 192 ~ 193
- Mass; 358 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.13 (3H, s), 4.80 (2H, d, J=5.2Hz), 5.95 (2H, s), 6.79 (1H, d, J=8.0Hz), 6.91 (1H, d, J=8.0Hz), 6.95 (1H, s), 8.05 (1H, d, J=8.8Hz), 8.17 (1H, d, J=8.8Hz), 8.72 (1H, s), 8.81 (1H, brs), 8.98 (1H, s)

Example 139

2-Hydroxymethyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



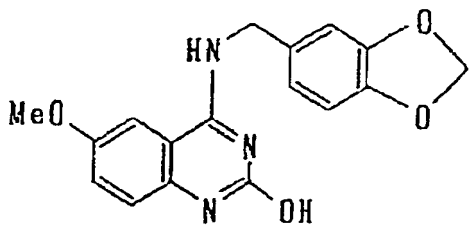
1.5 g of 10% palladium/carbon powder was added to a solution of 1.26 g (2.93 mmol) of 2-benzyloxymethyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline in an ethyl acetate/ethanol (20 ml - 20 ml) mixture. The obtained mixture was stirred at room temperature in a stream of hydrogen for 24 hours and filtered through Celite. The filter cake was washed with hot ethyl acetate/ethanol. The filtrate and the washings were distilled under a reduced pressure to remove the solvent. Thus 0.89 g of the title compound was obtained as a pale-yellow crystal.

- molecular formula; $C_{18}H_{17}N_3O_4$
- yield(%); 89
- m.p.(°C); 216 ~ 218
- Mass; 340 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.91 (3H, s), 4.15 (1H, brs), 4.68 (2H, brs), 4.77 (2H, d, J=5.6Hz), 5.95 (2H, s), 6.79 (1H, d, 7.6Hz), 6.85 (1H, brs), 6.88 (1H, dd, J=7.6Hz, 1.6Hz), 6.92 (1H, d, J=1.6Hz), 7.21 (1H, d, J=2.8Hz),

7.37 (1H, dd, J = 9.2Hz, 2.8Hz), 7.72 (1H, d, J = 9.2Hz)

Example 140

2-Hydroxy-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



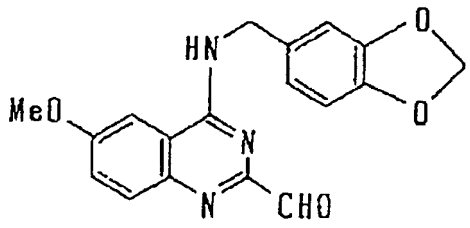
The title compound was prepared in a similar manner to that of Example 139.

- molecular formula; $C_{17}H_{15}N_3O_4$
- yield(%); 16
- m.p.(°C); 215 ~ 217 (dec.)
- Mass; 326 $(M+H)^+$
- NMR δ (DMSO-d_6);

  3.79 (3H, s), 4.62 (2H, d, J = 5.6Hz), 5.98 (2H, s), 6.84 ~ 6.87 (2H, m), 6.94 (1H, s), 7.09 (1H, d, J = 8.8Hz), 7.22 (1H, dd, J = 8.8Hz, 2.8Hz), 7.60 (1H, d, J = 2.8Hz), 8.65 (1H, brt, J = 5.6Hz), 10.55 (1H, s)

Example 141

2-Formyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



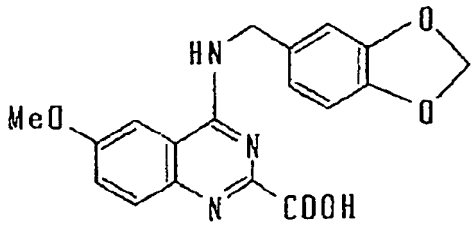
A solution of 1.5 ml of dimethyl sulfoxide in 5 ml of methylene chloride was dropped into a solution of 1.0 ml (11 mmol) of oxalyl chloride in 10 ml of methylene chloride under stirring at -78°C. The obtained mixture was stirred at -78°C for 15 minutes, followed by the dropwise addition of a solution of 0.74 g (2.2 mmol) of 2-hydroxymethyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline in 7 ml of dimethyl sulfoxide. After the mixture thus obtained had been stirred at -78°C for 20 minutes, 5 ml of triethylamine was dropped into the resulting mixture. The mixture thus prepared was stirred for 30 minutes, while raising the temperature to room temperature. Water was added to the reaction mixture and the resulting mixture was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to remove the solvent. Thus, 0.74 g of the title compound was obtained as a crude brown oil.

- molecular formula; $C_{18}H_{15}N_3O_4$
- yield(%); quantitative
- NMR δ ($CDCl_3$);

  3.93 (3H, s), 4.86 (2H, d, J = 5.6Hz), 5.95 (2H, s), 6.28 (1H, brs), 6.78 (1H, d, J = 8.0Hz), 6.89 (1H, dd, J = 8.0Hz, 1.6Hz), 6.92 (1H, d, J = 1.6Hz), 7.09 (1H, d, J = 2.8Hz), 7.47 (1H, dd, J = 9.2Hz, 2.8Hz), 7.97 (1H, d, J = 9.2Hz), 10.02 (1H, s)

Example 142

2-Carboxy-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



1.00 g of silver (I) oxide and 15 ml of a 1N aqueous solution of sodium hydroxide were added to a solution of 0.59 g (1.8 mmol) of the 2-formyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline prepared in Example 141 in 20 ml of 1,4-dioxane. The obtained mixture was stirred at 60 °C. After 30 minutes, the reaction mixture was filtered through Celite and the filter cake was washed with a small amount of dioxane and water. The filtrate and washings were neutralized with 1N hydrochloric acid and extracted with chloroform/ethanol. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to remove the solvent. The crystal thus formed was recovered by filtration and washed with chloroform to give 0.34 g of the title compound as a pale-yellow crystal.

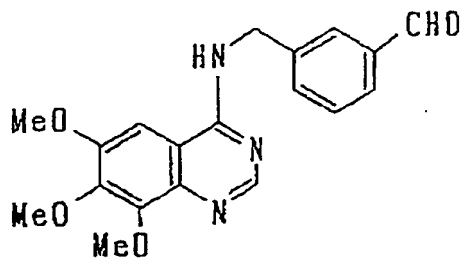
- molecular formula; $C_{18}H_{15}N_3O_5$
- yield(%); 55
- m.p.(°C); 190 ~ 191 (dec.)
- Mass; 354 $(M+H)^+$
- NMR δ (DMSO-d_6);
  3.90 (3H, s), 4.77 (2H, d, J = 5.6Hz), 5.97 (2H, s), 6.86 (1H, d, J = 8.0Hz), 6.92 (1H, d, J = 8.0Hz), 7.05 (1H, s), 7.49 (1H, dd, J = 9.2Hz, 2.8Hz), 7.76 (1H, d, J = 2.8Hz), 7.79 (1H, d, J = 9.2Hz), 8.91 (1H, brt, J = 5.6Hz)

Examples 143 to 145

The following compounds were prepared in a similar manner to that of Example 141 or 142.

Example 143

4-(3-Formylbenzyl)amino-6,7,8-trimethoxyquinazoline

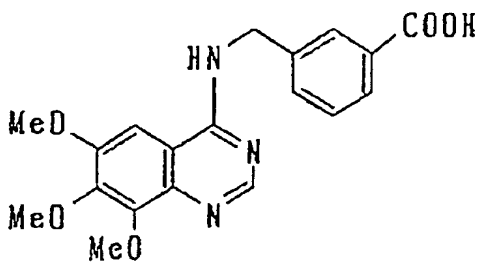


- molecular formula; $C_{19}H_{19}N_3O_4$
- yield(%); quantitative
- m.p.(°C); oily substance
- NMR δ ($CDCl_3$);
  3.96 (3H, s), 4.04 (3H, s), 4.13 (3H, s), 4.97 (2H, d, J = 5.6Hz), 5.97 (1H, brt, J = 5.6Hz), 6.76 (1H,

s), 7.53 (1H, t, J=7.6Hz), 7.70 (1H, d, J=7.6Hz), 7.81 (1H, d, J=7.6Hz), 7.91 (1H, s), 8.64 (1H, s), 10.00 (1H, s)

Example 144

4-(3-Carboxybenzyl)amino-6,7,8-trimethoxyquinazoline

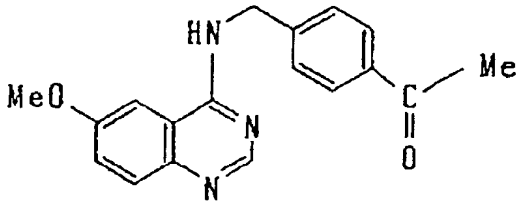


- molecular formula; $C_{19}H_{19}N_3O_5$
- yield(%); 45
- m.p.(°C); 245 ~ 246 (dec.)
- Mass; 370 $(M+H)^+$
- NMR δ (DMSO-d_6);

3.89 (3H, s), 3.93 (3H, s), 3.98 (3H, s), 4.86 (2H, d, J=5.6Hz), 7.46 (1H, d, J=7.6Hz), 7.56 (1H, s), 7.62 (1H, d, J=7.6Hz), 7.83 (1H, d, J=7.6Hz), 7.95 (1H, s), 8.39 (1H, s), 8.83 (1H, brs)

Example 145

4-(4-Acetylbenzyl)amino-6-methoxyquinazoline

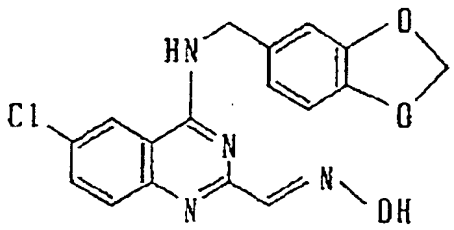


- molecular formula; $C_{18}H_{17}N_3O_2$
- yield(%); 41
- m.p.(°C); 204 ~ 206
- Mass; 308 $(M+H)^+$
- NMR δ ($CDCl_3$);

2.60 (3H, s), 3.91 (3H, s), 4.97 (2H, d, J=5.6Hz), 5.96 (1H, brs), 6.98 (1H, s), 7.42 (1H, d, J=9.2Hz), 7.50 (2H, d, J=8.0Hz), 7.82 (1H, d, J=9.2Hz), 7.94 (2H, d, J=8.0Hz), 8.61 (1H, s)

Example 146

2-Hydroxyiminomethyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



0.60 g of hydroxylamine hydrochloride and 3.0 ml of a 1N aqueous solution of sodium hydroxide were added to a solution of 1.00 g (2.93 mmol) of 2-formyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline in 30 ml of ethanol. The obtained mixture was stirred at 60 °C for 30 minutes and cooled by allowing to stand. The crystal thus precipitated was recovered by filtration, washed with ethanol and n-hexane and air-dried to give 1.00 g of the title compound as a white crystal.

- molecular formula; $C_{17}H_{13}N_4O_3Cl$
- yield(%); 96
- m.p.(°C); 245 ~ 246 (dec.)
- Mass; 357 (M + 1)
- NMR δ (DMSO-d_6);

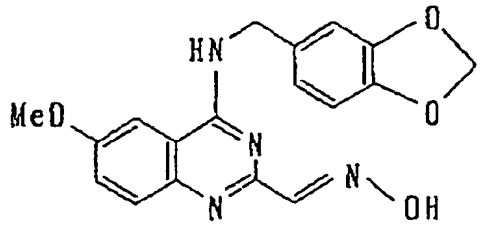
  4.69 (2H, d, J = 6.0Hz), 5.96 (2H, s), 6.84 (1H, d, J = 7.6Hz), 6.91 (1H, d, J = 7.6Hz, 1.6Hz), 7.05 (1H, d, J = 1.6Hz), 7.72 (1H, d, J = 8.8Hz), 7.78 (1H, dd, J = 8.8Hz, 2.0Hz), 7.96 (1H, s), 8.45 (1H, d, J = 2.0Hz), 8.91 (1H, brt, J = 6.0Hz), 11.83 (1H, s)

Examples 147 to 149

The following compounds were prepared in a similar manner to that of Example 146.

Example 147

2-Hydroxyiminomethyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline

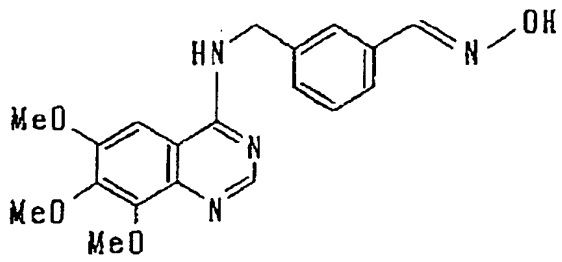


- molecular formula; $C_{18}H_{16}N_4O_4$
- yield(%); 46
- m.p.(°C); 229 ~ 230 (dec.)
- Mass; 353 $(M + H)^+$
- NMR δ (DMSO-d_6);

  3.88 (3H, s), 4.72 (2H, d, J = 5.6Hz), 5.96 (2H, s), 6.85 (1H, d, J = 8.0Hz), 6.91 (1H, d, J = 8.0Hz), 7.05 (1H, s), 7.40 (1H, dd, J = 9.2Hz, 2.8Hz), 7.66 (1H, d, J = 9.2Hz), 7.69 (1H, d, J = 2.8Hz), 7.94 (1H, s), 8.62 (1H, brt, J = 5.6Hz), 11.63 (1H, s)

Example 148

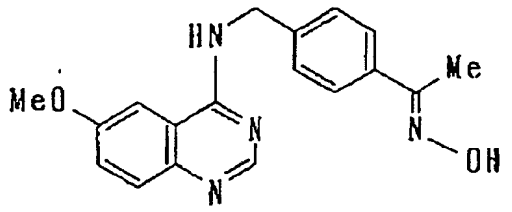
4-(3-Hydroxyiminomethylbenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{20}N_4O_4$
- yield(%); 56
- m.p.(°C); 231 ~ 232 (dec.)
- Mass; 369 $(M+H)^+$
- NMR δ (DMSO-d_6);
  3.88 (3H, s), 3.91 (3H, s), 3.98 (3H, s), 4.80 (2H, d, J=6.0Hz), 7.3 ~ 7.5 (3H, m), 7.52 (1H, s), 7.60 (1H, s), 8.11 (1H, s), 8.35 (1H, s), 8.60 (1H, brs), 11.17 (1H, s)

Example 149

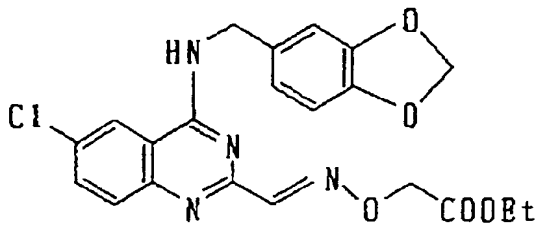
4-[4-(1-Hydroxyiminoethyl)benzyl]amino-6-methoxyquinazoline



- molecular formula; $C_{18}H_{18}N_4O_2$
- yield(%); quantitative
- m.p.(°C); 245 ~ 246 (dec.)
- Mass; 323 $(M+H)^+$
- NMR δ (DMSO-d_6);
  2.13 (3H, s), 3.95 (3H, s), 4.97 (2H, d, J=5.6Hz), 7.44 (2H, d, J=8.4Hz), 7.63 (2H, d, J=8.4Hz), 7.68 (1H, dd, J=9.2Hz, 2.8Hz), 7.83 (1H, d, J=9.2Hz), 8.14 (1H, d, J=2.8Hz), 8.84 (1H, s), 10.75 (1H, brs), 11.18 (1H, s)

Example 150

2-Ethoxycarbonylmethoxyiminomethyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



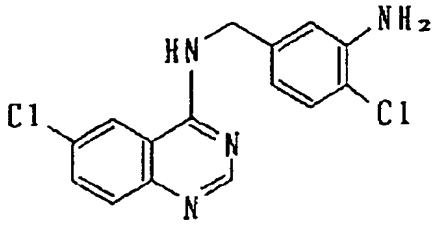
0.10 g (2.5 mmol) of sodium hydride was added to a suspension of 0.50 g (1.4 mmol) of 2-hydroxyiminomethyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline in 25 ml of dimethylformamide. The obtained mixture was stirred. After 30 minutes, 25 ml (2.3 mmol) of ethyl bromoacetate was dropped into the mixture. The mixture thus obtained was stirred at room temperature for several hours, followed by the addition of water. The obtained mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under a reducer pressure to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to give 0.52 g of the title compound as a pale-yellow crystal.

- molecular formula; $C_{21}H_{19}N_4O_5Cl$
- yield(%); 84
- m.p.(°C); 154 ~ 155
- Mass; 443 (M + 1)
- NMR δ ($CDCl_3$);

  1.29 (3H, t, J = 7.2Hz), 4.23 (2H, q, J = 7.2Hz), 4.74 (2H d, J = 5.2Hz), 4.88 (2H, s), 5.96 (2H, s), 6.03 (1H, brt, J = 5.2Hz), 6.78 (1H, d, J = 7.6Hz), 6.87 (1H, d, J = 7.6Hz, 1.6Hz), 6.93 (1H, d, J = 1.6Hz), 7.65 (1H, dd, J = 8.8Hz, 2.0Hz), 7.70 (1H, d, J = 2.0Hz), 7.84 (1H, d, J = 8.8Hz), 8.25 (1H, s)

Example 151

4-(3-Amino-4-chlorobenzyl)amino-6-chloroquinazoline



A mixture comprising 1.00 g (2.86 mmol) of 4-(4-chloro-3-nitrobenzyl)amino-6-chloroquinazoline, 0.85 g of powdered iron, 10 ml of acetic acid and 50 ml of ethanol was heated under reflux for several hours and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to give 0.91 g of the title compound as a pale-yellow crystal.

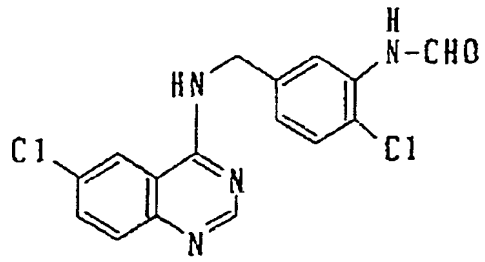
- molecular formula; $C_{15}H_{12}N_4Cl_2$
- yield(%); quantitative
- m.p.(°C); 226 ~ 229 (dec.)
- Mass; 319 $(M + H)^+$
- NMR δ ($CDCl_3$);

  4.19 (2H, brs), 4.73 (2H, d, J = 6.0Hz), 6.71 (1H, dd, J = 8.0Hz, 2.0Hz), 6.83 (1H, d, J = 2.0Hz), 7.18

(1H, d, J=8.0Hz), 7.64 (1H, dd, J=8.8Hz, 2.0Hz), 7.72 (1H, brs), 7.74 (1H, d, J=8.8Hz), 8.19 (1H, d, J=2.0Hz), 8.60 (1H, s)

Example 152

4-(4-Chloro-3-formamidobenzyl)amino-6-chloroquinazoline



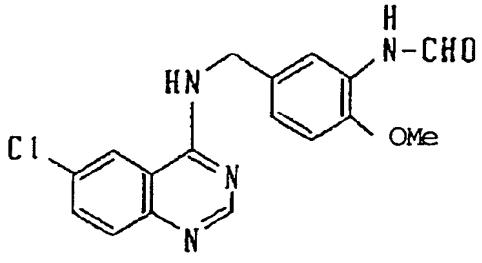
0.90 g (2.82 mmol) of the 4-(3-amino-4-chlorobenzyl)amino-6-chloroquinazoline prepared in Example 151 was dissolved in 15 ml of formic acid, followed by the addition of 1 ml of acetic anhydride. The obtained mixture was stirred at room temperature for several hours and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate) and recrystallized from ethyl acetate to give 0.64 g of the title compound as a pale yellow crystal.

- molecular formula; $C_{16}H_{12}N_4OCl_2$
- yield(%); 65
- m.p.(°C); 229 ~ 230
- Mass; 347 $(M+H)^+$
- NMR δ (DMSO-d_6);

4.74 (2H, d, J=5.6Hz), 7.15 (1H, dd, J=8.4Hz, 2.0Hz), 7.43 (1H, d, J=8.4Hz), 7.72 (1H, d, J=8.8Hz), 7.80 (1H, dd, J=8.8Hz, 2.0Hz), 8.16 (1H, d, J=2.0Hz), 8.32 (1H, d, J=2.0Hz), 8.45 (1H, s), 8.46 (1H, s), 8.95 (1H, brs), 9.83 (1H, brs)

Example 153

4-(3-Formamido-4-methoxybenzyl)amino-6-chloroquinazoline



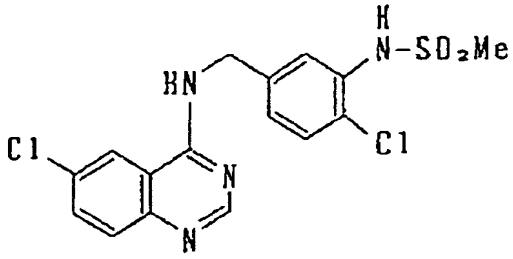
1 g of powdered iron was added in portions to a mixture comprising 1 g of 4-(3-nitro-4-methoxybenzyl)-amino-6-chloroguinazoline, 4 ml of acetic acid, 4 ml of water and 40 ml of ethanol, while heating the mixture under mild reflux. The obtained mixture was heated under reflux for 2 hours and filtered to remove insolubles. Concentrated hydrochloric acid was added in portions to the brown filtrate obtained above to give a yellow transparent solution. This solution was cooled with ice to precipitate crystals. The crystals were recovered by filtration and dried to give 1.1 g of 4-(3-amino-4-methoxybenzyl)amino-6-chloroquinazoline hydrochloride. This hydrochloride was dissolved in ethanol/water and the obtained solution was made alkaline by adding a 15% aqueous solution of sodium hydroxide in portions. Water was added to the resulting alkaline solution in portions to precipitate crystals. The crystals were recovered by

filtration, washed with water and dried to give 770 mg of 4-(3-amino-4-methoxybenzyl)amine-6-chloroquinazoline (an aniline derivative). Separately, 1 ml of formic acid was dropped into 2 ml of acetic anhydride under cooling with ice and the obtained mixture was heated at 50 °C for 15 minutes and immediately cooled with ice, followed by the addition of the above aniline derivative as such (in a crystalline state). The obtained mixture was reacted at that temperature for one hour and at room temperature for one hour, followed by the addition of water. The crystals thus formed were recovered by filtration, washed with water and dried to give 130 mg of the title compound.

- molecular formula; $C_{17}H_{15}N_4O_2Cl$ (342.786)
- yield(%); 60
- m.p.(°C); 208 ~ 209
- Mass; 343 $(MH)^+$
- NMR δ (DMSO-d_6);
  3.82 (3H, s), 4.68 (2H, d, J = 5.7Hz), 6.98 (1H, d, J = 8.2Hz), 7.09 (1H, dd, J = 2.0Hz, 8.2Hz), 7.71 (1H, d, J = 9.0Hz), 7.79 (1H, dd, J = 2.4Hz, 9.0Hz), 8.23 (1H, d, J = 2.0Hz), 8.27 (1H, d, J = 2.4Hz), 8.47 (2H, s), 8.88 (1H, t, J = 5.7Hz), 9.62 (1H, brs)

Example 154

4-(3-Methanesulfonylamino-4-chlorobenzyl)amino-6-chloroquinazoline



75 μl of methanesulfonyl chloride was added to a mixture comprising 100 mg of 4-(3-amino-4-chlorobenzyl)amino-6-chloroquinazoline and 3 ml of pyridine. The obtained mixture was stirred at room temperature for 1.5 hours. 20 ml of water was added in portions to the reaction mixture to precipitate crystals. The crystals were recovered by filtration, washed with water and dried to give 109 mg of the title compound.

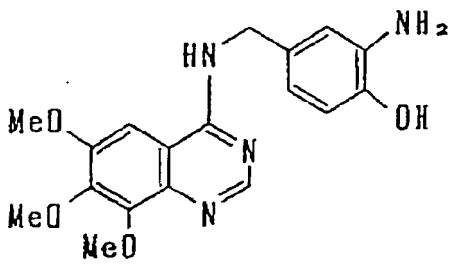
- molecular formula; $C_{16}H_{14}N_4O_2SCl_2$ (397.284)
- yield(%); 88
- m.p.(°C); 209 ~ 210
- Mass; 397 $(MH)^+$
- NMR δ (DMSO-d_6);
  3.01 (3H, s), 4.75 (2H, d, J = 5.7Hz), 7.23 (1H, dd, J = 2.2Hz, 8.2Hz), 7.45 (1H, d, J = 8.2Hz), 7.46 (1H, d, J = 2.2Hz), 7.73 (1H, d, J = 9.0Hz), 7.81 (1H, dd, J = 2.4Hz, 9.0Hz), 8.45 (1H, d, J = 2.4Hz), 8.47 (1H, s), 8.97 (1H, brt, J = 5.7Hz), 9.4 (1H, brs)

Examples 155 to 161

The following compounds were prepared in a similar manner to those of Examples 151 to 154.

Example 155

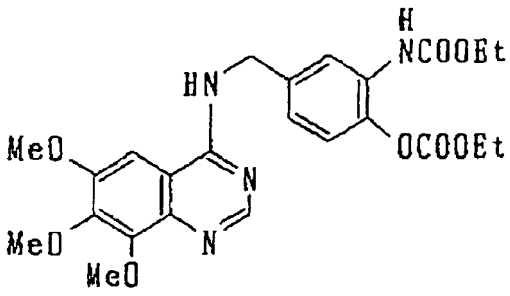
4-(3-Amino-4-hydroxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{20}N_4O_4$
- yield(%); quantitative
- m.p.(°C); amorphous
- Mass; 357 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.68 (1H, brs), 3.82 (1H, brs), 3.95 (3H, s), 4.02 (3H, s), 4.11 (3H, s), 4.68 (2H, d, J = 4.4Hz), 6.61 (1H, brs), 6.64 (1H, d, J = 7.6Hz), 6.77 (1H, d, J = 7.6Hz), 7.01 (1H, s), 8.50 (1H, brs), 8.60 (1H, s)

Example 156

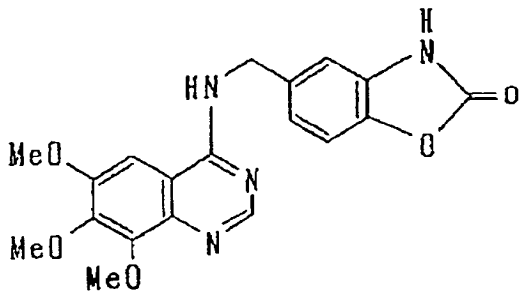
4-(3-Ethoxycarbonylamino-4-ethoxycarbonyloxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{24}H_{28}N_4O_8$
- yield(%); 54
- m.p.(°C); 229 ~ 230 (dec.)
- Mass; 501 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.31 (3H, t, J = 7.2Hz), 1.40 (3H, t, J = 7.2Hz), 3.95 (3H, s), 4.03 (3H, s), 4.11 (3H, s), 4.21 (2H, q, J = 7.2Hz), 4.35 (2H, q, J = 7.2Hz), 4.81 (1H, d, J = 5.2Hz), 5.80 (1H, brt, J = 5.2Hz), 6.74 (1H, s), 6.87 (1H, s), 7.13 (1H, d, J = 8.0Hz), 7.20 (1H, d, J = 8.0Hz), 8.18 (1H, brs), 8.64 (1H, s)

Example 157

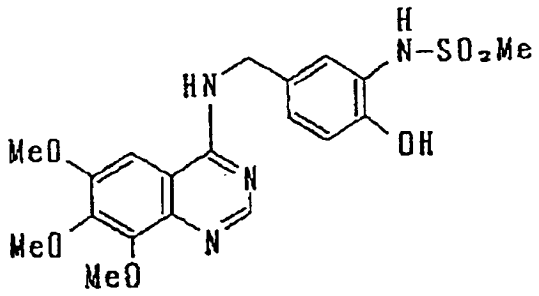
4-[Benzoxazol-2(3H)-on-5-ylmethyl]amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{18}N_4O_5$
- yield(%); 62
- m.p.(°C); 232 ~ 233 (dec.)
- Mass; 383 $(M+H)^+$
- NMR δ (DMSO-d_6);
  3.87 (3H, s), 3.90 (3H, s), 3.96 (3H, s), 4.78 (2H, d, J = 5.6Hz), 7.06 (1H, s), 7.07 (1H, d, J = 8.0Hz), 7.20 (1H, d, J = 8.0Hz), 7.50 (1H, s), 8.35 (1H, s), 8.58 (1H, brt, J = 5.6Hz), 11.48 (1H, brs)

Example 158

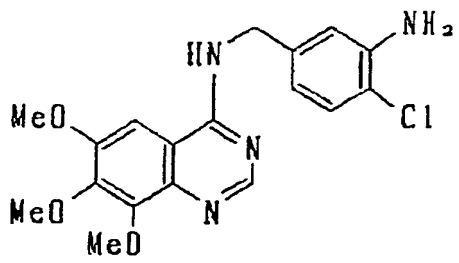
4-(4-Hydroxy-3-methanesulfonylaminobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{22}N_4O_6S$
- yield(%); 56
- m.p.(°C); 215 ~ 216 (dec.)
- Mass; 435 $(M+H)^+$
- NMR δ (DMSO-d_6);
  2.91 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 3.96 (3H, s), 4.65 (2H d, J = 5.6Hz), 6.83 (1H, d, J = 8.0Hz), 7.04 (1H, dd, J = 8.0Hz, 2.0Hz), 7.22 (1H, d, J = 2.0Hz), 7.50 (1H, s), 8.34 (1H, s), 8.52 (1H, brt, J = 5.6Hz), 8.66 (1H, brs), 9.75 (1H, brs)

Example 159

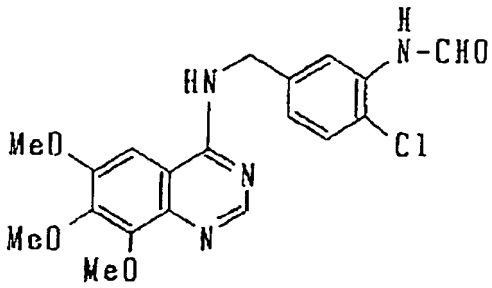
4-(3-Amino-4-chlorobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{18}H_{19}N_4O_3Cl$
- yield(%); 86
- m.p.(°C); 181 ~ 182 (dec.)
- Mass; 375 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.95 (3H, s), 4.03 (3H, s), 4.08 (2H, brs), 4.13 (3H, s), 4.75 (2H, d, J = 5.6Hz), 5.65 (1H, brs), 6.67 (1H, s), 6.72 (1H, dd, J = 8.0Hz, 2.0Hz), 6.81 (1H, d, J = 2.0Hz), 7.23 (1H, d, J = 8.0Hz), 8.65 (1H, s)

Example 160

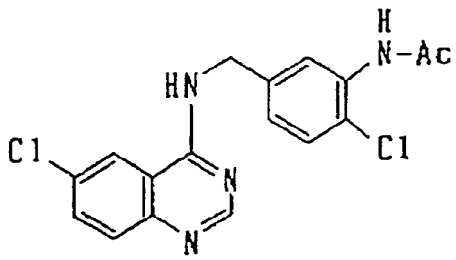
4-(4-Chloro-3-formamidobenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{19}N_4O_4Cl$
- yield(%); 68
- m.p.(°C); 202 ~ 204 (dec.)
- Mass; 403 $(M+H)^+$
- NMR δ ($DMSO-d_6$);
  3.88 (3H, s), 3.91 (3H, s), 3.98 (3H, s), 4.75 (2H, d, J = 5.6Hz), 7.14 (1H, dd, J = 8.4Hz, 2.0Hz), 7.42 (2H, d, J = 8.4Hz), 7.52 (1H, s), 8.15 (1H, d, J = 2.0Hz), 8.32 (1H, s), 8.35 (1H, s), 8.67 (1H, brs), 9.83 (1H, brs)

Example 161

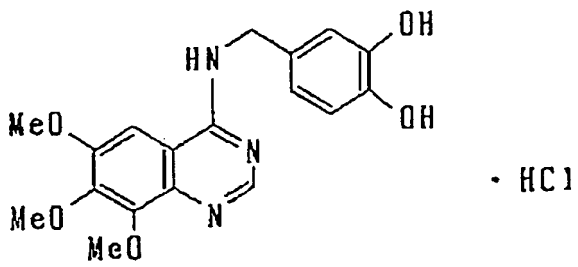
4-(3-Acetamido-4-chlorobenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{17}H_{14}N_4OCl_2$ (361.232)
- yield(%); 77
- m.p.(°C); 267 ~ 268
- Mass; 361 $(MH)^+$
- NMR δ (DMSO-d_6);
  2.06 (3H, s), 4.74 (2H, d, J = 5.7Hz), 7.17 (1H, dd, J = 2.0Hz, 8.2Hz), 7.42 (1H, d, J = 8.2Hz), 7.69 (1H, brs), 7.72 (1H, d, J = 9.0Hz), 7.81 (1H, dd, J = 2.4Hz, 9.0Hz), 8.45 (1H, d, J = 2.4Hz), 8.46 (1H, s), 8.96 (1H, brt, J = 5.7Hz), 9.48 (1H, brs)

Example 162

4-(3,4-Dihydroxybenzyl)amino-6,7,8-trimethoxyquinazoline hydrochloride

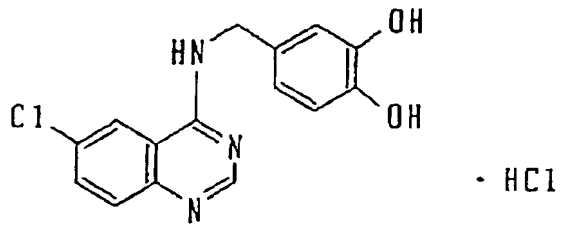


30 ml of a 1.0 M solution of boron trichloride in methylene chloride was dropped into a solution of 2.00 g (5.41 mmol) of 4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline in 150 ml of chloroform under stirring at room temperature. The obtained mixture was stirred at room temperature for 2 days, followed by the addition of methanol and the obtained mixture was distilled under a reduced pressure to remove the solvent. This procedure was repeated thrice and the obtained residue was purified by silica gel column chromatography (chloroform/n-hexane). Hydrochloric acid/ethanol was added to the eluate and the obtained mixture was distilled under a reduced pressure to remove the solvent, followed by the addition of ethanol. The crystals thus formed were recovered by filtration. Thus, 0.59 g of the title compound was obtained as a colorless needle.

- molecular formula; $C_{18}H_{19}N_3O_5 \cdot HCl$
- yield(%); 28
- m.p.(°C); 204 ~ 205 (dec.)
- Mass; 358 $(M+H)^+$
- NMR δ (DMSO-d_6);
  3.98 (3H, s), 3.99 (3H, s), 3.99 (3H, s), 4.78 (2H, d, J = 5.6Hz), 6.65 ~ 7.71 (2H, m), 6.79 (1H, s), 7.94 (1H, s), 8.71 (1H, s), 8.90 (2H, brs). 10.54 (1H, brs), 14.06 (1H, brs)

Example 163

4-(3,4-Dihydroxybenzyl)amino-6-chloroquinazoline hydrochloride

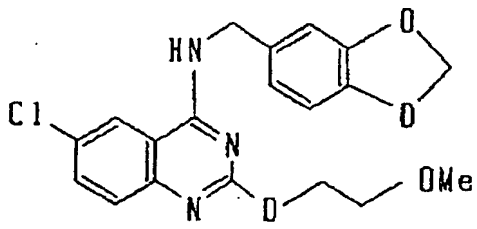


40 ml of a 1.0 M solution of boron trichloride in methylene chloride was dropped into a solution of 2.00 g (6.37 mmol) of 4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline in 150 ml of chloroform under stirring at room temperature. The obtained mixture was stirred at room temperature for 2 days, followed by the addition of methanol, and the obtained mixture was distilled under a reduced pressure to remove the solvent. This procedure was repeated twice. The crystals thus precipitated were washed with methanol and recrystallized from ethanol to give 1.53 g of the title compound as a yellow crystal.

- molecular formula; $C_{15}H_{12}N_3O_2Cl \cdot HCl$
- yield(%); 71
- m.p.(°C); 154 ~ 155 (dec.)
- Mass; 302 $(M+H)^+$
- NMR δ (DMSO-d_6);
  4.74 (2H, d, J=5.6Hz), 7.67 (1H, dd, J=8.0Hz, 2.0Hz), 6.70 (1H, d, J=8.0Hz), 6.81 (1H, d, J=2.0Hz), 7.87 (1H, d, J=8.8Hz), 8.02 (1H, dd, J=8.8Hz, 2.0Hz), 8.76 (1H, d, J=2.0Hz), 8.85 (1H, s), 8.90 (2H, brs), 10.42 (1H, brs)

Example 164

2-(2-Methoxyethoxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



A mixture comprising 20 ml of ethylene glycol monomethyl ether and 70 mg of 55% sodium hydride was heated to 100°C, followed by the addition of a mixture comprising 500 mg of 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline and 5 ml of ethylene glycol monomethyl ether. The obtained mixture was heated under reflux for 2 hours and poured into 50 ml of water. The obtained mixture was extracted with 50 ml of ethyl acetate twice. The organic layers were together washed with 70 ml of an aqueous solution of sodium chloride twice, dried over magnesium sulfate and concentrated under a reduced pressure to give a crystalline residue. This residue was reprecipitated from ethyl acetate/n-hexane to give 420 mg of the title compound.

- molecular formula; $C_{19}H_{18}N_3O_4Cl$
- yield(%); 75
- m.p.(°C); 138 ~ 139
- Mass; 388 $(M+1)^+$

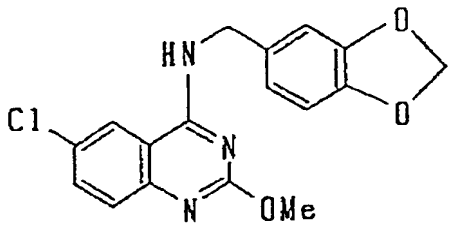
- NMR δ ($CDCl_3$);
  3.43 (3H, s), 3.78 ~ 3.81 (2H, m), 4.57 ~ 4.61 (2H, m), 4.73 (2H, d, J = 5.2Hz), 5.72 (1H, br), 5.96 (2H, s), 6.79 ~ 6.87 (3H, m), 7.52 ~ 7.58 (3H, m)

Examples 165 to 177

The following compounds were prepared in a similar manner to those of Examples 162 to 164.

Example 165

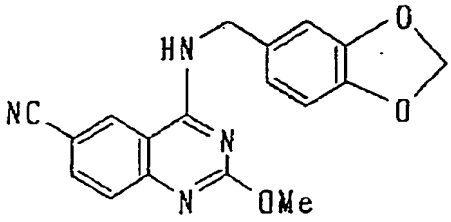
2-Methoxy-4-(3,4-methylenediokybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{17}H_{14}N_3O_3Cl$
- yield(%); 15
- m.p.(°C); 187 ~ 189
- Mass; 344 $(M+1)^+$
- NMR δ ($CDCl_3$);
  4.03 (3H, s), 4.50 (2H, d, J = 5.6Hz), 5.91 (1H, br), 5.96 (2H, s), 6.78 (1H, d, J = 7.6Hz), 6.81 (1H, dd, J = 7.6Hz, 1.6Hz), 6.82 (1H, d, J = 1.6Hz), 7.58 ~ 7.60 (3H, m)

Example 166

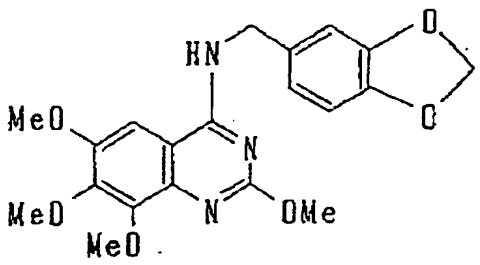
2-Methoxy-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



- molecular formula; $C_{18}H_{14}N_4O_3$ (334)
- yield(%); 23
- m.p.(°C); 224 (dec.)
- Mass; 335 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.87 (3H, s), 4.60 (2H, brs), 5.95 (2H, s), 6.84 (2H, s), 6.95 (1H, s), 7.55 (1H, d, J = 8.8Hz), 7.94 (1H, dd, J = 8.8Hz, 1.6Hz), 8.83 (1H, d, J = 1.6Hz), 9.18 (1H, br)

Example 167

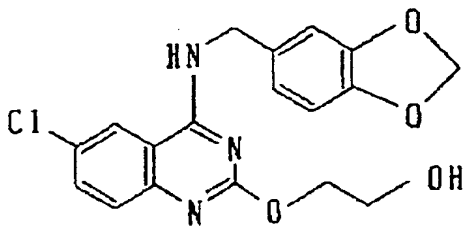
2,6,7,8-Tetramethoxy-4-(3,4-methylenedioxybenzyl)aminoquinazoline



- molecular formula; $C_{20}H_{21}N_3O_6$
- yield(%); 28
- m.p.(°C); 128 ~ 129
- Mass; 400 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.91 (3H, s), 4.04 (3H, s), 4.07 (3H, s), 4.14 (3H, s), 4.75 (2H, d, J=5.2Hz), 5.51 (1H, brs), 5.97 (2H, s), 6.60 (1H, s), 6.80 (1H, d, J=8.0Hz), 6.87 (1H, dd, J=8.0Hz, 2.0Hz), 6.90 (1H, d, J=2.0Hz)

Example 168

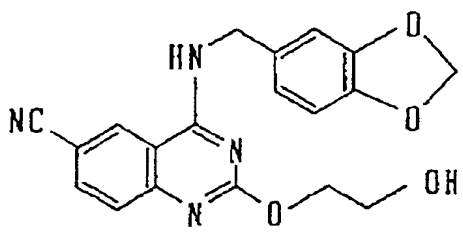
2-(2-Hydroxyethoxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{18}H_{16}N_3O_4Cl$ (373.5)
- yield(%); 97
- m.p.(°C); 191 ~ 193
- Mass; 374 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.65 ~ 3.69 (2H, m), 4.27 (2H, dd, J=8.8Hz, 5.6Hz), 4.60 (2H, d, J=5.2Hz), 4.82 (1H, t, J=5.6Hz), 5.95 (2H, s), 6.81 ~ 6.84 (2H, m), 6.92 (1H, s), 7.47 (1H, d, J=8.8Hz), 7.65 (1H, dd, J=8.8Hz, 2.2Hz), 8.34 (1H, d, J=2.2Hz), 8.82 (1H, br)

Example 169

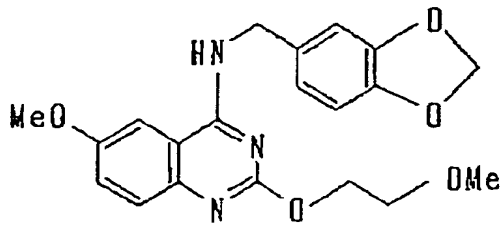
2-(2-Hydroxyethoxy)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



- molecular formula; $C_{19}H_{16}N_4O_4$ (364)
- yield(%); 94
- m.p.(°C); 227 ~ 229
- Mass; 365 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.68 (2H, t, J=5.2Hz), 4.30 (2H, t, J=5.2Hz), 4.44 (1H, brs), 5.97 (2H, s), 6.82 (2H, s), 6.95 (1H, s), 7.54 (1H, d, J=8.4Hz), 7.95 (1H, dd, J=8.4Hz, 1.6Hz), 8.78 (1H, d, J=1.6Hz), 9.04 (1H, br)

Example 170

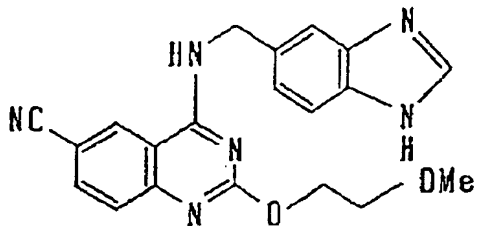
2-(2-Methoxyethoxy)-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



- molecular formula; $C_{20}H_{21}N_3O_5$ (383)
- yield(%); 68
- m.p.(°C); 118 ~ 119
- Mass; 384 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.26 (3H, s), 3.60 (2H, t, J=4.8Hz), 3.61 (3H, s), 4.33 (2H, t, J=4.8Hz), 4.63 (2H, d, J=6.0Hz), 5.95 (2H, s), 6.81 (1H, d, J=7.6Hz), 6.84 (1H, dd, J=7.6Hz, 0.4Hz), 6.91 (1H, d, J=0.4Hz), 7.29 (1H, dd, J=8.8Hz, 2.8Hz), 7.40 (1H, d, J=8.8Hz), 7.63 (1H, d, J=2.8Hz), 8.62 (1H, br)

Example 171

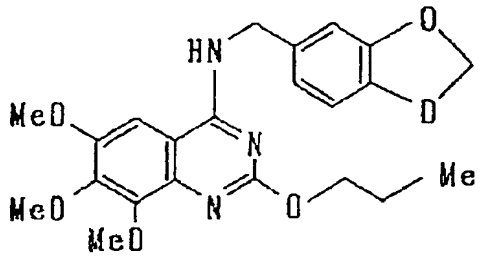
2-(2-Methoxyethoxy)-4-(benzimidazol-5-yl)methylamino-6-cyanoquinazoline



- molecular formula; $C_{20}H_{18}N_6O_2$ (374)
- yield(%); 68
- m.p.(°C); 267 (dec.)
- Mass; 375 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.21 (3H, s), 3.60 (2H, s), 4.40 (2H, s), 4.82 (2H, s), 7.17 ~ 7.66 (4H, m), 7.94 (1H, d, J=9.6Hz), 8.16 (1H, s), 8.81 (1H, s), 9.15 (1H, br)

Example 172

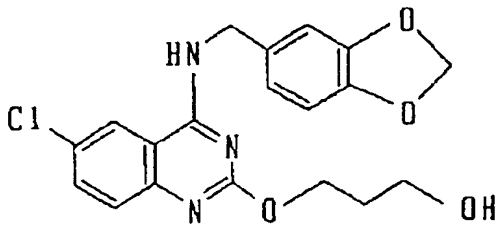
2-Propoxy-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{22}H_{25}N_3O_6$
- yield(%); 6
- m.p.(°C); 122 ~ 123
- Mass; 428 $(M+H)^+$
- NMR δ ($CDCl_3$);
  1.05 (3H, t, J=7.4Hz), 1.89 (2H, m), 3.90 (3H, s), 4.03 (3H, s), 4.13 (3H, s), 4.41 (2H, t, J=7.0Hz), 4.76 (2H, d, J=5.2Hz), 5.49 (1H, brs), 5.97 (2H, s), 6.60 (1H, s), 6.80 (1H, d, J=8.0Hz), 6.87 (1H, d, J=8.0Hz), 6.90 (1H, s)

Example 173

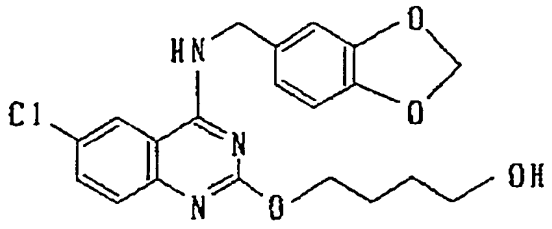
2-(3-Hydroxypropoxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{19}H_{18}N_3O_4Cl$ (387.5)
- yield(%); 60
- m.p.(°C); 118 ~ 120
- Mass; 388 $(M+1)^+$
- NMR δ ($CDCl_3$);
  2.02 (2H, tt, J=5.6Hz, 5.6Hz), 3.70 (2H, t, J=5.6Hz), 3.95 (1H, br), 4.66 (2H, t, J=5.6Hz), 4.71 (2H, d, J=5.2Hz), 5.95 (2H, s), 6.08 (1H, br), 6.77 (1H, d, J=8.0Hz), 6.83 (1H, d, J=8.0Hz), 6.85 (1H, s), 7.51 (1H, d, J=8.8Hz), 7.56 (1H, dd, J=8.8Hz, 2.0Hz), 7.61 (1H, d, J=2.0Hz)

Example 174

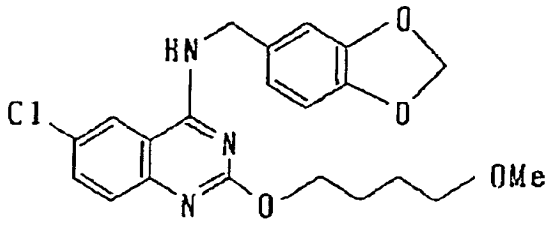
2-(4-Hydroxybutoxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{20}N_3O_4Cl$ (401.5)
- yield(%); 23
- m.p.(°C); 121 ~ 124
- Mass; 402 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.47 ~ 1.73 (4H, m), 3.40 ~ 3.47 (2H, m), 4.20 (2H, t, J=6.7Hz), 4.55 (2H, d, J=5.2Hz), 5.72 (2H, s), 6.56 (1H, d, J=8.0Hz), 6.66 (1H, dd, J=8.0Hz, 1.6Hz), 6.71 (1H, d, J=1.6Hz), 7.30 (2H, s), 7.88 (1H, brt, J=5.2Hz), 7.99 (1H, s)

Example 175

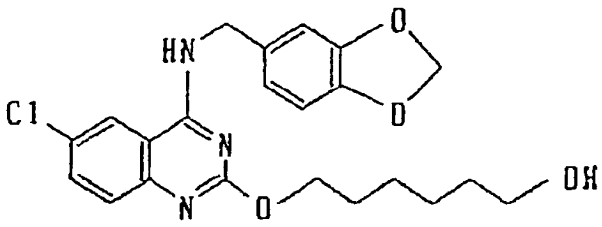
2-(4-Methoxybutoxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{22}N_3O_4Cl$ (415.5)
- yield(%); 26
- m.p.(°C); 120 ~ 123
- Mass; 416 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.77 (2H, tt, J=8.8Hz, 6.8Hz), 1.90 (2H, tt, J=8.8Hz, 6.8Hz), 3.34 (3H, s), 3.44 (2H, t, J=6.8Hz), 4.44 (2H, t, J=6.8Hz), 4.72 (2H, d, J=5.2Hz), 5.71 (1H, br), 5.96 (2H, s), 6.79 (1H, d, J=8.0Hz), 6.84 (1H, dd, J=8.0Hz, 1.8Hz), 6.87 (1H, d, J=1.8Hz), 7.53 ~ 7.59 (3H, m)

Example 176

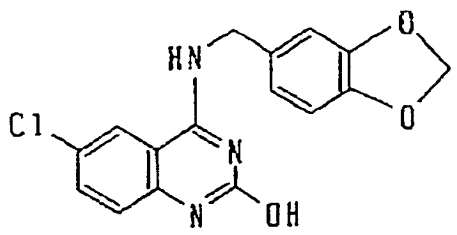
2-(6-Hydroxybenzyloxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{22}H_{24}N_3O_4Cl$ (429.5)
- yield(%); 66
- m.p.(°C); 144 ~ 146
- Mass; 430 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.14 ~ 1.40 (6H, m), 1.58 ~ 1.64 (2H, m), 3.06 (1H, br), 3.38 (2H, br), 4.17 (2H, t, J=6.8Hz), 4.52 (2H, d, J=5.6Hz), 5.73 (2H, s), 6.56 (1H, d, J=8.0Hz), 6.66 (1H, dd, J=8.0Hz, 1.6Hz), 6.71 (1H, d, J=1.6Hz), 7.30 (2H, s), 7.85 (1H, br), 7.96 (1H, s)

Example 177

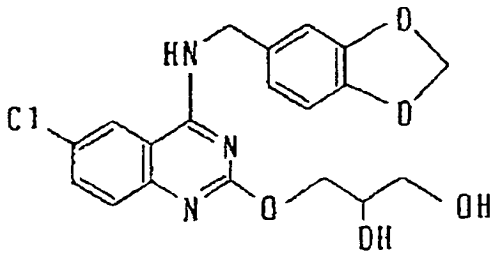
2-Hydroxy-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{16}H_{12}N_3O_3Cl$ (329.5)
- m.p.(°C); 257 (dec.)
- NMR δ (DMSO-d_6);
  4.668 (2H, d, J=5.6Hz), 5.967 (2H, s), 6.846 ~ 6.905 (2H, m), 6.995 (1H, s), 7.821 ~ 7.859 (2H, m), 8.508 (1H, s), 10.103 (1H, br), 11.916 (1H, s)

Example 178

2-(2,3-Dihydroxypropyl)oxy-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

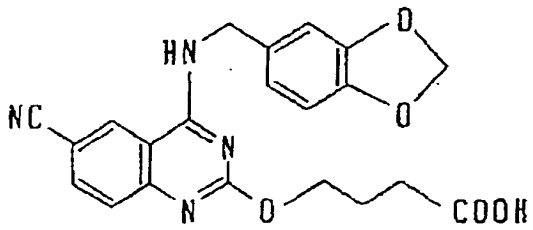


100 mg of sodium hydride was added to a mixture comprising 300 mg of 5-hydroxy-2-phenyl-1,3-dioxane and 5 ml of dimethylformamide. The obtained mixture was heated to 80°C. After the bubbling had been discontinued, 300 mg of 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline was added in a crystalline state. The obtained mixture was heated at 140°C for 2 hours and cooled, followed by the addition of water. The obtained, mixture was extracted with ethyl acetate. The extract was purified by silica gel column chromatography using an ethyl acetate/benzene mixture to give 118 mg of 2-(2-phenyl-1,3-dioxan-5-yl)oxy-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline. 100 mg of this compound was hydrolyzed with concentrated hydrochloric acid/ethanol by a conventional process to give 60 mg of the title compound through rearrangement.

- molecular formula; $C_{19}H_{18}ClN_3O_5$
- yield(%); 73
- m.p.(°C); 106 ~ 107
- Mass; 404 (MH^+)
- NMR δ (DMSO-d_6);
  3.42 (2H, t, J=5.7Hz), 3.79 (1H, sextet, J=5Hz), 4.17 (1H, dd, J=6.6Hz, 11.0Hz), 4.31 (1H, dd, J=4.2Hz, 11.0Hz), 4.63 (2H, d, J=5.7Hz), 4.66 (1H, t, J=6.0Hz), 4.94 (1H, d, J=5.3Hz), 5.98 (2H, s), 6.85 (2H, s), 6.95 (1H, s), 7.49 (1H, d, J=9.0Hz), 7.68 (1H, dd, J=2.4Hz, 9.0Hz), 8.37 (1H, d, J=2.4Hz), 8.83 (1H, t, J=5.7Hz)

Example 179

2-(3-Carboxypropyl)oxy-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



250 μl of dimethyl sulfoxide was slowly dropped into a mixture comprising 150 μl of oxalyl chloride and 15 ml of methylene chloride which had been preliminarily cooled in a dry ice/acetone bath. After 10 minutes, a solution of 500 mg of 2-(2-hydroxyethyl)oxy-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline in 1 ml of dimethyl sulfoxide was dropped into the mixture prepared above at the same temperature and after 10 minutes, 1.4 ml of N,N-diisopropylethylamine was dropped thereinto at the same temperature. The obtained mixture was stirred at the same temperature for 10 minutes and brought to room temperature. After 20 minutes, 600 mg of ethoxycarbonylmethylenetriphenylphosphorane was added in a crystalline state to the resulting mixture to conduct a reaction for 30 minutes, followed by the addition of water. The obtained mixture was extracted with ethyl acetate and the extract was purified by silica gel column chromatography using an ethyl acetate/benzene mixture to give 400 mg of 2-(3-ethoxycarbonyl-2-propenyl)oxy-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline (cis/trans mixture).

The whole of the above compound was dissolved in 30 ml of ethyl acetate and catalytically reduced with a 10% palladium/carbon catalyst under normal pressure. The reaction mixture was purified by silica gel column chromatography using an ethyl acetate/benzene mixture to give 250 mg of 2-(3-ethoxycarbonyl-propyl)oxy-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline (a saturated ester).

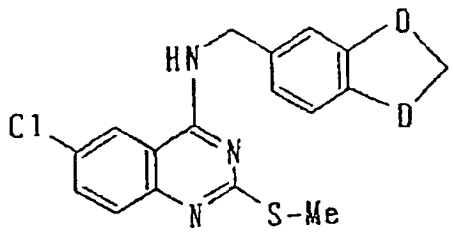
250 mg of the above saturated ester was dissolved in 50 ml of ethanol, followed by the addition of 1.7 ml of a 1N aqueous solution of sodium hydroxide. The obtained mixture was reacted at room temperature for 10 hours and then at 40 °C for 2 hours, cooled and neutralized by the addition of 1.7 ml of 1N aqueous hydrochloric acid, followed by the addition of water. The crystals thus formed were recovered by filtration and recrystallized from ethanol/water to give 200 mg of the title compound.

- molecular formula; $C_{21}H_{18}N_4O_5$ (406.398)
- yield(%); 86
- m.p.(°C); >290
- Mass; 407 (MH^+)
- NMR δ (DMSO);

  1.93 (2H, quintet, J=7Hz), 2.35 (2H, t, J=7.3Hz), 4.32 (2H, t, J=6.6Hz), 4.64 (2H, d, J=5.7Hz), 5.98 (2H, s), 6.87 (2H, s), 6.97 (1H, s), 7.56 (1H, d, J=8.8Hz), 7.96 (1H, dd, J=1.8Hz, 8.8Hz), 8.80 (1H, d, J=1.8Hz), 9.05 (1H, t, J=5.7Hz)

Example 180

2-Methylthio-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

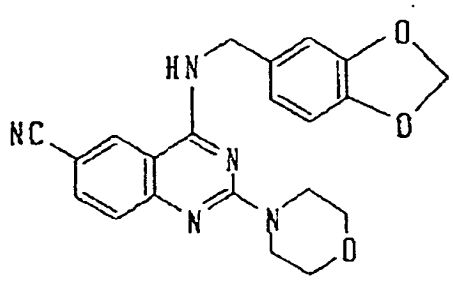


20 ml of N,N-dimethylformamide and 221 mg of sodium thiomethoxide were added to 1 g of 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline. The obtained mixture was stirred at 110 °C for one hour, neutralized with 1N hydrochloric acid and stirred at room temperature for one hour, followed by the addition of water. The crystals thus precipitated were recovered by filtration to give 780 mg of the title compound.

- molecular formula; $C_{17}H_{14}ClN_3O_2S$
- yield(%); 76
- m.p.(°C); 214 ~ 216
- Mass m/e; 360 (M + 1)
- NMR δ ($CDCl_3$);
  2.66 (3H, s), 4.85 (2H, d, J = 5.6Hz), 5.93 (2H, s), 6.73 (1H, d, J = 8.0Hz), 6.89 (1H, d, J = 8.0Hz), 6.93 (1H, s), 7.64 (1H, dd, J = 8.8Hz, 2.0Hz), 8.16 (1H, d, J = 8.8Hz), 8.77 (1H, d, J = 2.0Hz)

Example 181

2-Morpholino-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



A mixture comprising 338 mg of 2-chloro-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline, 435 mg of morpholine and 20 ml of isopropyl alcohol was heated under reflux for 3 hours, followed by the addition of 30 ml of water under heating. The precipitate thus formed was recovered by filtration and washed with 30 ml of water and 30 ml of ethyl acetate. Thus, 310 mg of the title compound was obtained.

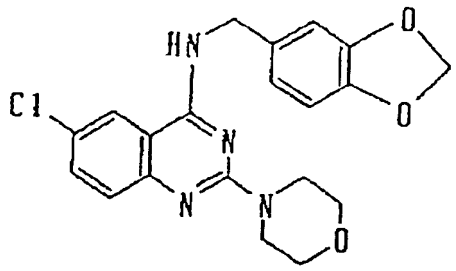
- molecular formula; $C_{21}H_{19}N_5O_3$ (389)
- yield(%); 80
- m.p.(°C); 270 ~ 272 (dec.)
- Mass; 390 $(M + 1)^+$
- NMR δ (DMSO-d_6);
  3.57 - 3.61 (4H, m), 3.73 ~ 3.79 (4H, m), 4.57 (2H, d, J = 5.6Hz), 5.95 (2H, s), 6.82 (1H, d, J = 8.0Hz), 6.85 (1H, d, J = 8.0Hz), 6.93 (1H, s), 7.27 (1H, d, J = 8.8Hz), 7.74 (1H, dd, J = 8.8Hz, 1.6Hz), 8.56 (1H, d, J = 1.6Hz), 8.75 (1H, brt, J = 5.6Hz)

Examples 182 to 183

The following compounds were prepared in a similar manner to that of Example 181.

Example 182

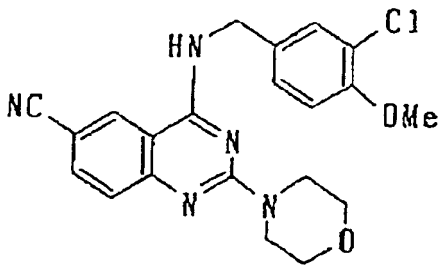
2-Morpholino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{19}N_4O_3Cl$ (398.850)
- yield(%); 96
- m.p.(°C); 208 ~ 209
- Mass; 399 $(MH)^+$
- NMR δ (DMSO-d_6);
  3.61 (4H, t, J=5Hz), 3.72 (4H, t, J=5Hz), 4.58 (2H, d, J=5.7Hz), 5.97 (2H, s), 6.85 (2H, s), 6.95 (1H, s), 7.28 (1H, d, J=9.0Hz), 7.51 (1H, dd, J=2.4Hz, 9.0Hz), 8.18 (1H, d, J=2.4Hz), 8.60 (1H, t, J=5.7Hz)

Example 183

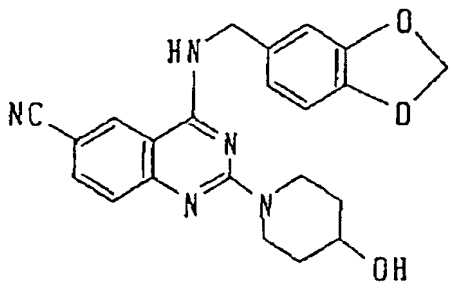
2-Morpholino-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline



- molecular formula; $C_{21}H_{20}N_5O_2Cl$ (407.5)
- yield(%); 51
- m.p.(°C); 222 ~ 223
- Mass; 410 $(M+1)^+$
- NMR δ (DMSO-d_6);
  3.56 ~ 3.61 (4H, m), 3.74 ~ 3.80 (4H, m), 3.80 (3H, s), 4.58 (2H, d, J=5.2Hz), 7.27 ~ 7.32 (2H, m), 7.44 (1H, d, J=1.6Hz), 7.75 (1H, dd, J=8.8Hz, 1.6Hz), 8.55 (1H, d, J=1.6Hz), 8.80 (1H, brt, J=5.2Hz)

Example 184

2-(4-Hydroxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



A mixture comprising 339 mg of 2-chloro-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline, 500 mg of 4-hydroxypiperidine and 20 ml of N,N-dimethylformamide was heated under reflux for 5 hours and poured into 50 ml of water, followed by the addition of 50 ml of ethyl acetate. The obtained mixture was filtered to remove insolubles. The organic layer of the filtrate was dried over magnesium sulfate and concentrated under a reduced pressure to give a crystalline residue. This residue was washed with chloroform to give 145 mg of the title compound.

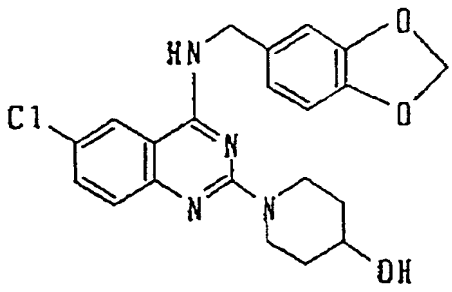
- molecular formula; $C_{22}H_{21}N_5O_3$ (403)
- yield(%); 36
- m.p.(°C); 229
- Mass; 404 $(M+1)^+$
- NMR δ (DMSO-d_6);
  1.19 ~ 1.30 (2H, m), 1.64 ~ 1.77 (2H, m), 3.21 ~ 3.30 (2H, m), 3.63 ~ 3.75 (1H, m), 4.34 ~ 4.38 (2H, m), 4.55 (2H, d, J=5.6Hz), 4.66 (1H, d, J=4.0Hz), 5.94 (2H, s), 6.80 ~ 6.86 (2H, m), 6.93 (1H, d, J=0.8Hz), 7.24 (1H, d, J=8.4Hz), 7.70 (1H, dd, J=8.4Hz, 1.6Hz), 8.52 (1H, d, J=1.6Hz), 8.70 (1H, br)

Examples 185 to 191

The following compounds were prepared in a similar manner to that of Example 184.

Example 185

2-(4-Hydroxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

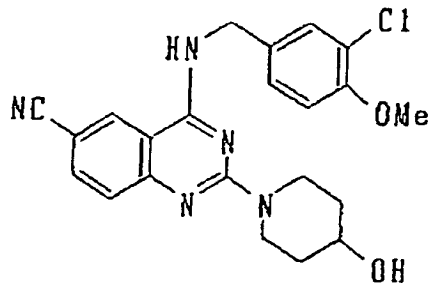


- molecular formula; $C_{21}H_{21}N_4O_3Cl$ (412.877)
- yield(%); 56
- m.p.(°C); 157 ~ 158
- Mass; 413 (MH^+)

- NMR δ (DMSO-d_6);
  1.2 ~ 1.3 (2H, m), 1.6 ~ 1.8 (2H, m), 3.1 ~ 3.2 (2H, m), 3.6 ~ 3.7 (1H, m), 4.3 ~ 4.4 (2H, m), 4.55 (2H, d, J = 5.7Hz), 4.65 (1H, d, J = 4.4Hz), 5.96 (2H, s), 6.84 (2H, s), 6.95 (1H, s), 7.24 (1H, d, J = 9.0Hz), 7.47 (1H, dd, J = 2.4Hz, 9.0Hz), 8.13 (1H, d, J = 2.4Hz), 8.53 (1H, t, J = 5.7Hz)

Example 186

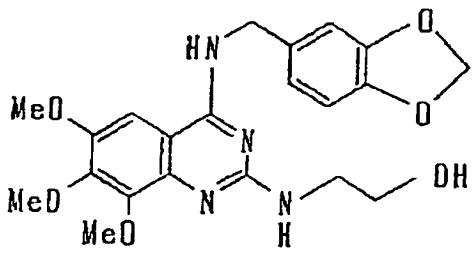
2-(4-Hydroxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline



- molecular formula; $C_{22}H_{22}N_5O_2Cl$ (423.5)
- yield(%); 80
- m.p.(°C); 207 ~ 208
- Mass; 424 $(M+1)^+$
- NMR δ (DMSO-d_6);
  1.18 ~ 1.30 (2H, m), 1.65 ~ 1.76 (2H, m), 3.21 ~ 3.33 (2H, m), 3.30 (3H, s), 3.64 ~ 3.72 (1H, m), 4.29 ~ 4.37 (2H, m), 4.57 (2H d, J = 5.6Hz), 4.66 (1H, d, J = 1.8Hz), 7.07 (1H, d, J = 8.4Hz), 7.24 (1H, d, J = 8.8Hz), 7.29 (1H, dd, J = 8.4Hz, 2.0Hz), 7.43 (1H, d, J = 2.0Hz), 7.71 (1H, dd, J = 8.8Hz, 2.0Hz), 8.51 (1H, d, J = 2.0Hz), 8.74 (1H, brt, J = 1.8Hz)

Example 187

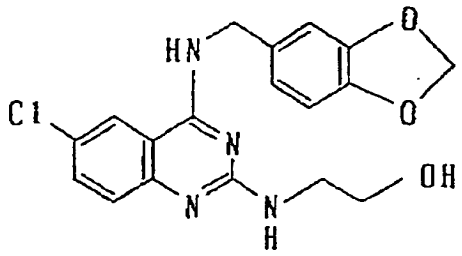
2-(2-Hydroxyethyl)amino-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{24}N_4O_6$
- yield(%); 38
- m.p.(°C); amorphous
- Mass; 429 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.60 (2H, m), 3.88 (3H, s & 1H, m), 3.99 (3H, s), 4.01 (3H, s), 4.67 (2H, d, J = 5.6Hz), 5.32 (1H, brs), 5.53 (1H, brs), 5.97 (2H, s), 6.55 (1H, s), 6.80 (1H, d, J = 8.0Hz), 6.85 (1H, d, J = 8.0Hz), 6.89 (1H, s)

Example 188

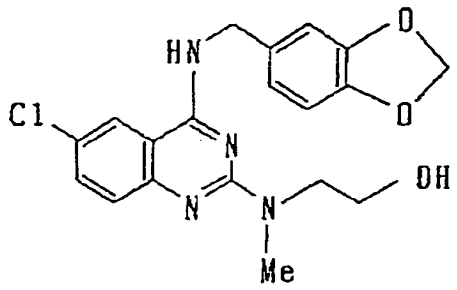
2-(2-Hydroxyethyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{18}H_{17}N_4O_3Cl$
- yield(%); 47
- m.p.(°C); 138 ~ 139
- Mass m/e; 373 (M + 1)
- NMR δ ($CDCl_3$(+ DMSO-d_6));
  3.60 (2H, m), 3.79 (2H, t, J = 4.8Hz), 4.65 (2H, d, J = 5.2Hz), 5.94 (2H, s), 6.76 (1H, d, J = 8.0Hz), 6.85 (1H, dd, J = 8.0Hz, 2.0Hz), 6.90 (1H, d, J = 2.0Hz), 7.34 (1H, d, J = 8.8Hz), 7.44 (1H, dd, J = 8.8Hz, 2.4Hz), 8.02 (2H, brs)

Example 189

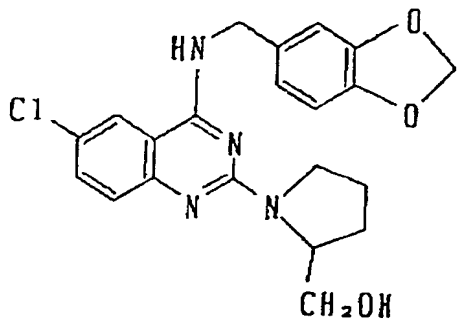
2-[N-(2-Hydroxyethyl)-N-methylamino]-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{19}H_{19}N_4O_3Cl$
- yield(%); 48
- m.p.(°C); 146 ~ 148
- Mass m/e; 387 (M + 1)
- NMR δ ($CDCl_3$(+ DMSO-d_6));
  3.27 (3H, s), 3.82 (2H, t, J = 4.8Hz), 3.89 (2H, t, J = 4.8Hz), 4.67 (2H, d, J = 5.6Hz), 5.95 (2H, s), 6.77 (1H, d, J = 8.0Hz), 6.86 (1H, dd, J = 8.0Hz, 1.6Hz), 6.90 (1H, d, J = 1.6Hz), 7.43 (2H, m), 7.76 (1H, brs)

Example 190

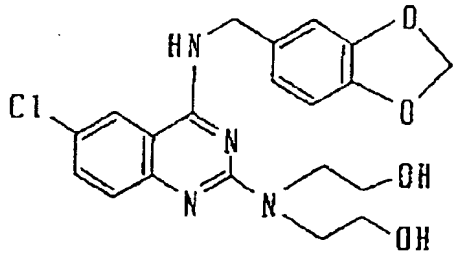
2-(2-Hydroxymethylpyrrolidin-1-yl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{21}N_4O_3Cl$ (412.877)
- yield(%); 70
- m.p.(°C); 182 ~ 183
- Mass; 413 (MH^+)
- NMR δ (DMSO-d_6);
  1.8 ~ 2.0 (4H, br 2 peaks), 3.4 ~ 3.7 (3H, br 2 peaks), 4.1 ~ 4.2 (1H, brs), 4.58 (2H, d, J=5.8Hz), 5.96 (2H, s), 6.84 (1H, d, J=8.0Hz), 6.88 (1H, dd, J=1.3Hz, 8.0Hz), 6.96 (1H, d, J=1.3Hz), 7.23 (1H, d, J=8.8Hz), 7.47 (1H, dd, J=2.4Hz, 8.8Hz), 8.15 (1H, d, J=2.4Hz), 8.4 ~ 8.6 (1H, brs)

Example 191

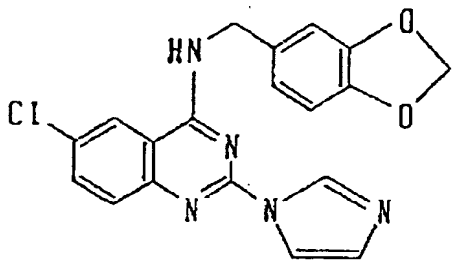
2-Bis(2-hydroxyethyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{21}N_4O_4Cl$ (416.865)
- yield(%); 56
- m.p.(°C); 167 ~ 168
- Mass; 417 (MH^+)
- NMR δ (DMSO-d_6);
  3.5 ~ 3.7 (8H, br 2 peaks), 4.56 (2H, d, J=5.7Hz), 5.96 (2H, s), 6.85 (2H, s), 6.93 (1H, s), 7.22 (1H, d, J=9.0Hz), 7.47 (1H, dd, J=2.4Hz, 9.0Hz), 8.15 (1H, d, J=2.4Hz), 8.55 (1H, brt, J=5.7Hz)

Example 192

2-(1-Imidazolyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



103 mg of imidazole was added to a suspension of 66 mg of sodium hydride in 6 ml of dimethylformamide at 0 °C. The obtained mixture was stirred for 10 minutes. 500 mg of 2,6-dichloro-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline was added to the resulting mixture at room temperature. The mixture thus prepared was stirred at 100 °C for 20 minutes, followed by the addition of water. The crystals precipitated were recovered by filtration and washed with water and ethanol/acetone successively to give 325 mg of the title compound.

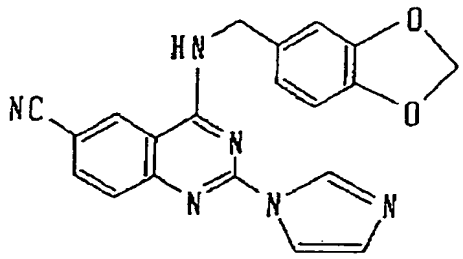
- molecular formula; $C_{19}H_{14}N_5O_2Cl$
- yield(%); 59
- m.p.(°C); 275 ~ 276 (dec.)
- Mass m/e; 380 (M + 1)
- NMR δ (DMSO-d_6);
  4.74 (2H, d, J = 5.6Hz), 5.96 (2H, s), 6.85 (1H, d, J = 8.0Hz), 6.95 (1H, dd, J = 8.0Hz, 1.6Hz), 7.03 (1H, d, J = 1.6Hz), 7.08 (1H, d, J = 1.2Hz), 7.68 (1H, d, J = 8.8Hz), 7.78 (1H, dd, J = 8.8Hz, 2.4Hz), 7.94 (1H, d, J = 1.2Hz), 8.47 (1H, d, J = 2.4Hz), 8.58 (1H, t, J = 2.4Hz), 9.28 (1H, t, J = 5.6Hz)

Examples 193 to 197

The following compounds were prepared in a similar manner to that of Example 192.

Example 193

2-(Imidazol-1-yl)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline

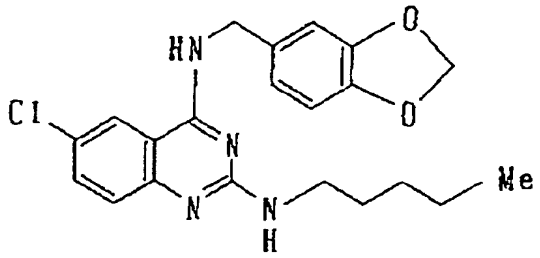


- molecular formula; $C_{20}H_{14}N_6O_2$ (370)
- yield(%); 81
- m.p.(°C); >290
- Mass; 371 $(M + 1)^+$
- NMR δ (DMSO-d_6);
  4.74 (2H, d, J = 6.0Hz), 5.95 (2H, s), 6.86 (1H, d, J = 8.0Hz), 6.95 (1H, dd, J = 8.0Hz, 1.6Hz), 7.04 (1H, d, J = 1.6Hz), 7.09 (1H, d, J = 1.6Hz), 7.73 (1H, d, J = 8.4Hz), 7.95 (1H, d, J = 1.6Hz), 8.06 (1H, dd,

J = 8.4Hz, 1.6Hz), 8.61 (1H, d, J = 1.6Hz), 8.87 (1H, d, J = 1.6Hz), 9.47 (1H, brt, J = 6.0Hz)

Example 194

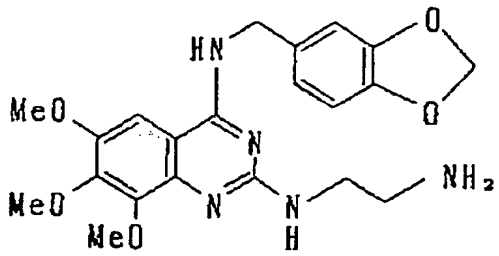
2-Pentylamino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{23}N_4O_2Cl$
- yield(%); 97
- m.p.(°C); 194 ~ 195
- Mass m/e; 399 (M + 1)
- NMR δ ($CDCl_3$);
  0.86 (3H, t, J = 7.2Hz), 1.29 (4H, m), 1.58 (2H, quintet, J = 6.8Hz), 3.47 (2H, q, J = 6.8Hz), 4.78 (2H, d, J = 5.6Hz), 5.87 (2H, s), 6.66 (1H, d, J = 8.0Hz), 6.89 (1H, d, J = 8.0Hz), 6.94 (1H, s), 7.26 (1H, d, J = 8.8Hz), 7.41 (1H, d, J = 8.8Hz), 7.90 (1H, t, J = 5.6Hz), 8.55 (1H, s), 9.53 (1H, brs)

Example 195

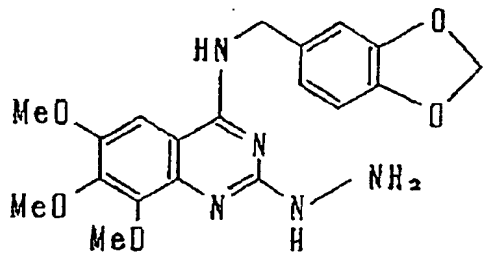
2-(2-Aminoethyl)amino-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{21}H_{25}N_5O_5$
- yield(%); 87
- m.p.(°C); amorphous
- Mass; 428 $(M + H)^+$
- NMR δ ($CDCl_3$);
  1.44 (2H, s), 2.93 (2H, t, J = 6.0Hz), 3.57 (2H, brs), 3.88 (3H, s), 4.00 (3H, s), 4.07 (3H, s), 4.70 (2H, d, J = 4.8Hz), 5.16 (1H, brs), 5.51 (1H, brs), 5.96 (2H, s), 6.56 (1H, s), 6.80 (1H, d, J = 8.0Hz), 6.86 (1H, d, J = 8.0Hz), 6.90 (1H, s)

Example 196

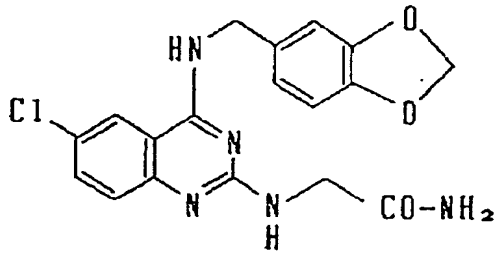
2-Hydrazino-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{19}H_{21}N_5O_5$
- yield(%); 12
- m.p.(°C); oily substance
- Mass; 400 $(M+H)^+$
- NMR δ ($CDCl_3$);
  3.88 (3H, s), 3.99 (3H, s), 4.05 (3H, s), 4.66 (2H, d, J=3.6Hz), 5.92 (2H, s), 6.75 (1H, d, J=8.0Hz), 6.83 (1H, d, J=8.0Hz), 6.87 (1H, s), 7.04 (2H, brs)

Example 197

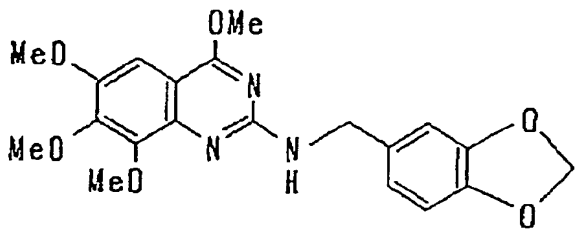
2-(Carbamoylmethyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{18}H_{16}N_5O_3Cl$
- yield(%); 63
- m.p.(°C); 259 ~ 260 (dec.)
- Mass m/e; 386 (M+1)
- NMR δ (DMSO-d_6);
  4.02 (2H, d, J=4.8Hz), 4.66 (2H, d, J=5.6Hz), 5.97 (2H, s), 6.86 (1H, d, J=8.0Hz), 6.91 (1H, d, J=8.0Hz), 6.99 (1H, s), 7.19 (1H, s), 7.50 (1H, d, J=8.8Hz), 7.61 (1H, s), 7.83 (1H, d, J=8.8Hz), 8.09 (1H, brs), 8.49 (1H, brs), 10.03 (1H, brs)

Example 198

2-(3,4-Methylenedioxybenzyl)amino-4,6,7,8-tetramethoxyquinazoline



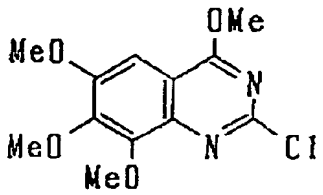
1.00 g (3.51 mmol) of 2-chloro-4,6,7,8-tetramethoxyquinazoline, 0.60 g (3.97 mmol) of piperonylamine and 0.60 g of sodium carbonate were mixed with 30 ml of isopropyl alcohol. The obtained mixture was heated under reflux for 24 hours and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to give 0.12 g of the title compound as an oily substance.

- molecular formula; $C_{20}H_{21}N_3O_6$
- yield(%); 9
- m.p.(°C); oily substance
- NMR δ ($CDCl_3$);

  3.91 (3H, s), 4.02 (3H, s), 4.04 (6H, s), 4.63 (2H, d, J=6.0Hz), 5.30 (1H, brs), 5.93 (2H, s), 6.75 (1H, d, J=8.0Hz), 6.86 (1H, dd, J=8.0Hz, 1.6Hz), 6.92 (1H, d, J=1.6Hz), 7.06 (1H, s)

Example 199

2-Chloro-4,6,7,8-tetramethoxyquinazoline



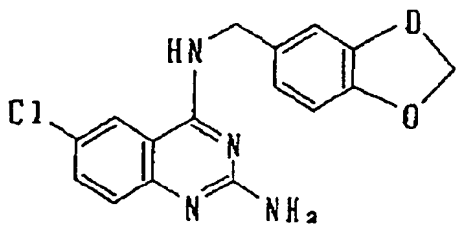
5.00 g (17.3 mmol) of 2,4-dichloro-6,7,8-trimethoxyquinazoline was suspended in 100 ml of methanol, followed by the gradual addition of 1.5 g of sodium hydride. The obtained mixture was heated under reflux. After several hours, the reaction mixture was concentrated under a reduced pressure, followed by the addition of water. The crystal thus precipitated was recovered by filtration, washed with water and air-dried to give 4.80 g of the title compound as a pale-pink crystal.

- yield(%); 97
- m.p.(°C); 119 ~ 120
- Mass; 285 $(M+1)^+$
- NMR δ ($CDCl_3$);

  3.98 (3H, s), 4.06 (3H, s), 4.12 (3H, s), 4.19 (3H, s), 7.17 (1H, s)

Example 200

2-Amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



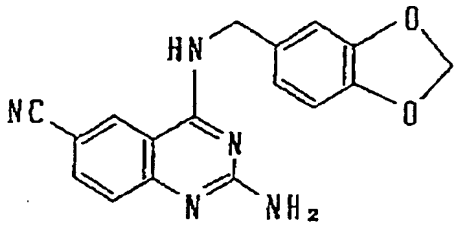
2.0 g of 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline was heated to 120 °C in 50 ml of ethanolic ammonia put in a pressure vessel for 18 hours, cooled and concentrated under a reduced pressure. The obtained residue was introduced to a silica gel column and eluted with a chloroform/methanol (9 : 1) mixture to give 830 mg of the title compound.

- molecular formula; $C_{16}H_{13}N_4O_2Cl$
- yield(%); 44
- m.p.(°C); 285 (dec.)
- Mass; 329 $(M+1)^+$
- NMR δ ($CDCl_3$);

  4.67 (2H, d, J = 5.6Hz), 4.98 (2H, br), 5.74 (1H, br), 5.96 (2H, s), 6.78 (1H, d, J = 7.6Hz), 6.83 (1H, dd, J = 7.6Hz, 1.6Hz), 6.86 (1H, d, J = 1.6Hz), 7.38 (1H, d, J = 9.6Hz), 7.46 ~ 7.49 (2H, m)

Example 201

2-Amino-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



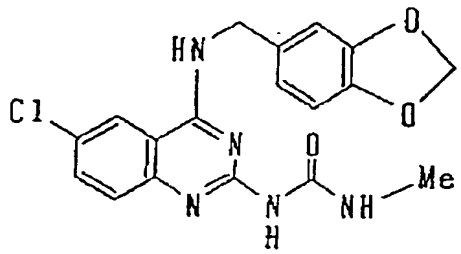
The title compound was prepared in a similar manner to those of Examples 199 and 200.

- molecular formula; $C_{17}H_{13}N_5O_2$ (319)
- yield(%); 60
- m.p.(°C); 284 (dec.)
- Mass; 320 $(M+1)^+$
- NMR δ ($CDCl_3$);

  4.31 (2H, d, J = 5.6Hz), 5.25 (2H, brs), 5.58 (2H, s), 6.40 (1H, d, J = 7.6Hz), 6.51 (1H, dd, J = 7.6Hz, 1.2Hz), 6.57 (1H, d, J = 1.2Hz), 6.95 (1H, d, J = 8.4Hz), 7.25 (1H, dd, J = 8.4Hz, 1.6Hz), 8.00 (1H, br), 8.20 (1H, d, J = 1.6Hz)

Example 202

2-(Methylcarbamoyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



4 ml of dimethyl sulfoxide and 260 mg of methyl isocyanate were added to 500 mg of 2-amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline. The obtained mixture was stirred at 50 °C for 3 hours and distilled under a reduced pressure to remove excess methyl isocyanate, followed by the addition of chloroform and water. The mixture thus obtained was filtered and the filtrate was extracted with chloroform twice. The organic layers were combined, washed with water twice, dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (benzene/acetone) and recrystallized (from benzene/chloroform/ethanol) to give 72 mg of the title compound.

- molecular formula; $C_{18}H_{16}N_5O_3Cl$
- yield(%); 12
- m.p.(°C); 245 ~ 247
- Mass m/e; 386 (M + 1)
- NMR δ (DMSO-d_6);

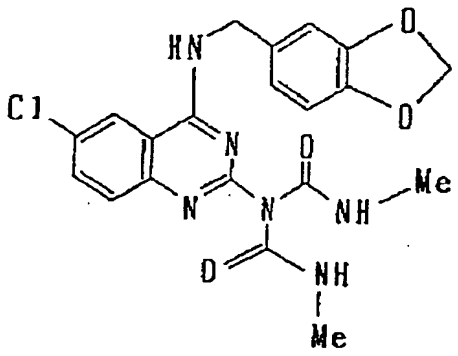
2.75 (3H, d, J = 4.4Hz), 4.56 (2H, d, J = 6.0Hz), 5.95 (2H, s), 6.82 (1H, d, J = 8.4Hz), 6.92 (1H, d, J = 8.4Hz), 7.11 (1H, s), 7.56 (1H, d, J = 8.8Hz), 7.67 (1H, dd, J = 8.8Hz, 1.6Hz), 8.27 (1H, d, J = 1.6Hz), 8.90 (1H, t, J = 6.0Hz), 9.20 (1H, s), 9.38 (1H, d, J = 4.4Hz)

Examples 203 and 204

The following compounds were prepared in a similar manner to that of Example 202.

Example 203

2-Bis(methylcarbamoyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



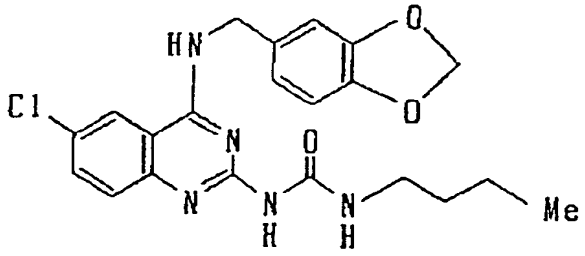
- molecular formula; $C_{20}H_{19}N_6O_4Cl$
- yield(%); 8

- amt. of product (mg); 45
- m.p.(°C); 243 ~ 245
- Mass m/e; 443 (M+1)
- NMR δ (DMSO-d_6);

2.71 (6H, d, J=4.8Hz), 4.53 (2H, d, J=6.0Hz), 5.94 (2H, s), 6.80 (1H, d, J=8.0Hz), 6.85 (1H, d, J=8.0Hz), 6.95 (1H, s), 7.66 (1H, d, J=8.8Hz), 7.72 (1H, dd, J=8.8Hz, 2.0Hz), 8.32 (1H, dd, J=2.0Hz), 8.85 (1H, dd, J=4.8Hz), 9.01 (1H, t, J=6.0Hz)

Example 204

2-(n-Butylcarbamoyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

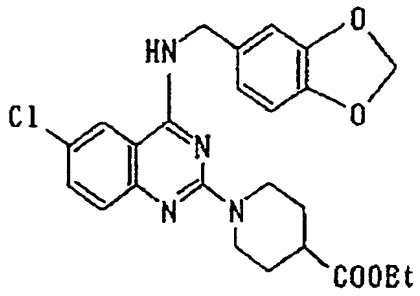


- molecular formula; $C_{21}H_{22}N_5O_3Cl$
- yield(%); 40
- m.p.(°C); 209 ~ 210
- Mass m/e; 428 (M+1)
- NMR δ (DMSO-d_6);

0.89 (3H, t, J=7.2Hz), 1.33 (2H, sextet, J=7.2Hz), 1.45 (2H, quintet, J=7.2Hz), 3.18 (2H, t, J=7.2Hz), 4.56 (2H, d, J=6.0Hz), 5.95 (2H, s), 6.83 (1H, d, J=8.0Hz), 6.91 (1H, d, J=8.0Hz), 7.09 (1H, s), 7.46 (1H, d, J=8.8Hz), 7.66 (1H, dd, J=8.8Hz, 2.0Hz), 8.27 (1H, d, J=2.0Hz), 8.90 (1H, t, J=6.0Hz), 9.17 (1H, s), 9.58 (1H, t, J=7.2Hz)

Example 205

2-(4-Ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



3.61 g of methyl isonipecotate, 2.32 g of triethylamine and 5 ml of 2-propanol were added to 1 g of 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinazoline prepared in Example 92. The obtained mixture was refluxed for 100 minutes. The mixture thus obtained was extracted with chloroform twice. The organic layers were combined, washed with water, dried over magnesium sulfate and freed from the solvent by distillation. The residue was recrystallized (from ethanol/water) to give 1.31 g of the title compound.

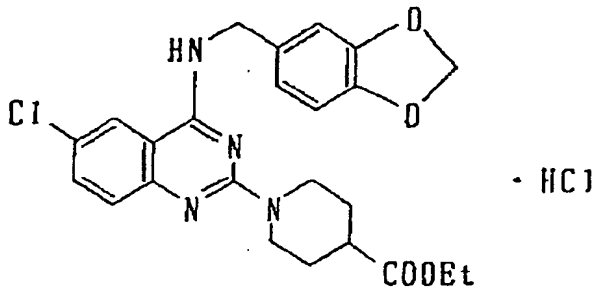
- molecular formula; $C_{24}H_{25}ClN_4O_4$
- yield(%); 97

- m.p.(°C); 118 ~ 119
- Mass; 469 (M + 1)
- NMR δ (DMSO-d_6);

1.18 (3H, t, J = 7.2Hz), 1.42 (2H, m), 2.58 (1H, m), 2.98 (2H, m), 4.06 (2H, q, J = 7.2Hz), 4.56 (2H, m, J = 5.6Hz), 4.62 (2H, m), 5.96 (2H, s), 6.82 (1H, d, J = 8.0Hz), 6.86 (1H, dd, J = 8.0Hz, 1.6Hz), 6.94 (1H, d, J = 1.6Hz), 7.26 (1H, d, J = 9.2Hz), 7.48 (1H, dd, J = 9.2Hz, 2.4Hz), 8.15 (1H, d, J = 2.4Hz), 8.56 (1H, brt, J = 5.6Hz)

Example 206

2-(4-Ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride



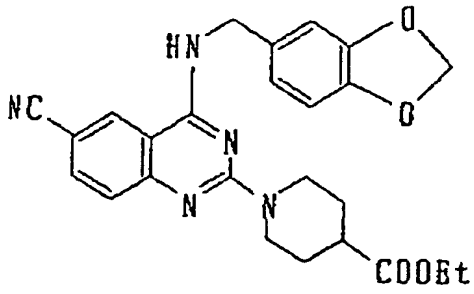
The title compound was prepared from the 2-(4-Ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline prepared in Example 205 by the use of ethanol-hydrochloric acid-ethanol.

- molecular formula; $C_{24}H_{25}ClN_4O_4 \cdot HCl$
- yield(%); 97
- m.p.(°C); 174 ~ 175
- NMR δ (DMSO-d_6);

1.20(3H, t, J = 7.2Hz), 1.59(2H, m), 1.97(2H, m), 2.75(1H, m), 3.31(2H, m), 4.09(2H, q, J = 7.2Hz), 4.53(2H, m), 4.67(2H, d, J = 5.6Hz), 5.98(2H, s), 6.86(1H, d, J = 8.0Hz), 6.90(1H, dd, J = 8.0Hz, 1.6Hz), 7.01(1H, d, J = 1.6Hz), 7.83(1H, dd, J = 8.8Hz, 2.0Hz), 7.91 (1H, d, J = 8.8Hz), 8.52(1H, d, J = 2.0Hz), 10.15(1H, brs), 12.28(1H, brs)

Example 207

2-(4-Ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



3.71 g of ethyl isonipecotate, 2.38 g of triethylamine and 10 ml of 2-propanol were added to 1 g of 2-chloro-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline. The obtained mixture was refluxed for 1 hour and cooled to room temperature. The crystals thus precipitated were recovered by filtration and washed with water and ether successively to give 1.126 g of the title compound.

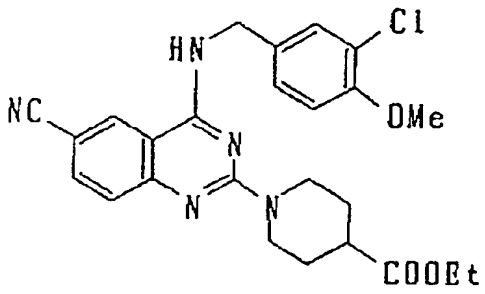
- molecular formula; $C_{25}H_{25}N_5O_4$

- yield(%); 83
- m.p.(°C); 192 ~ 193
- Mass; 460 (M + 1)
- NMR δ ($CDCl_3$);

1.26 (3H, t, J = 7.2Hz), 1.71 (2H, m), 1.99 (2H, m), 2.59 (1H, m), 3.12 (2H, brt, J = 12.0Hz), 4.15 (2H, q, J = 7.2Hz), 4.67 (2H, d, J = 5.2Hz), 4.82 (2H, dt, J = 13.2Hz, 3.6Hz), 5.96 (2H, s), 6.79 (1H, d, J = 8.0Hz), 6.85 (1H, dd, J = 8.0Hz, 1.6Hz), 6.88 (1H, d, J = 1.6Hz), 7.42 (1H, brs), 7.61 (1H, dd, J = 8.8Hz, 1.6Hz), 7.84 (1H, brs)

Example 208

2-(4-Ethoxycarbonylpiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline



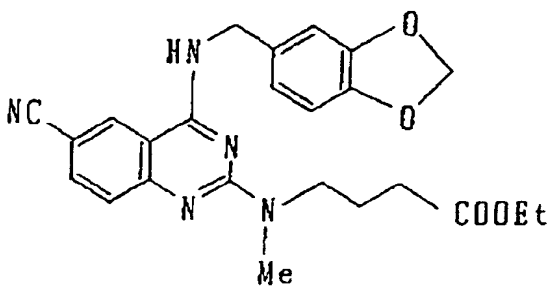
3.5 g of ethyl isonipecotate, 2.25 g of triethylamine and 30 ml of 2-propanol were added to 1 g of 2-chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline. The obtained mixture was refluxed for 30 minutes and cooled to room temperature. The crystals thus precipitated were recovered by filtration and washed with water and ethanol successively to give 1.13 g of the title compound.

- molecular formula; $C_{25}H_{26}N_5O_3Cl$
- yield(%); 85
- m.p.(°C); 202 ~ 203
- Mass; 480 (M + 1)
- NMR δ ($CDCl_3$);

1.26 (3H, t, J = 7.2Hz), 1.72 (2H, m), 1.99 (2H, m), 2.59 (1H, m), 3.13 (2H, brt, J = 11.2Hz), 3.90 (3H, s), 4.15 (2H, q, J = 7.2Hz), 4.69 (2H, d, J = 5.6Hz), 4.80 (2H, m), 6.91 (1H, d, J = 8.4Hz), 7.25 (1H, dd, J = 8.4Hz, 2.4Hz), 7.42 (1H, d, J = 2.4Hz), 7.43 (1H, brs), 7.61 (1H, dd, J = 8.8Hz, 1.6Hz), 7.87 (1H, brs)

Example 209

2-[N-(3-Ethoxycarbonylpropyl)-N-methylamino]-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



858 mg of ethyl N-methyl-4-aminobutyrate hydrochloride, 238 mg of triethylamine, 4 ml of 2-propanol and 2 ml of N,N-dimethylformamide were added to 400 mg of 2-chloro-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline. The obtained mixture was refluxed for 1 hour, cooled to room temperature and filtered. The filtrate was distilled under a reduced pressure to remove the solvent and the residue was recrystallized (from ethanol/water) to give 410 mg of the title compound.

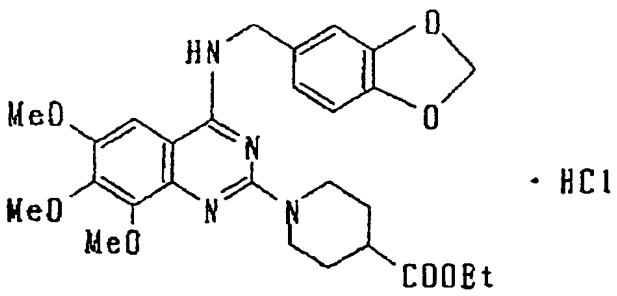
- molecular formula; $C_{24}H_{25}N_5O_4$
- yield(%); 78
- m.p.(°C); 152 ~ 153
- Mass; 448 (M + 1)
- NMR δ ($CDCl_3$);
  1.22 (3H, t, J = 6.8Hz), 1.97 (2H, brs), 2.30 (2H, brs), 3.24 (3H, s), 3.75 (2H, brs), 4.10 (2H, q, J = 6.8Hz), 4.68 (2H, d, J = 5.2Hz), 5.96 (2H, s), 6.79 (1H, d, J = 8.0Hz), 6.84 (1H, d, J = 8.0Hz), 6.87 (1H, s), 7.42 (1H, brs), 7.60 (1H, d, J = 8.8Hz), 7.81 (1H, brs)

Examples 210 to 221

The following compounds were prepared in a similar manner to that of Examples 205 to 209.

Example 210

2-(4-Ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline hydrochloride

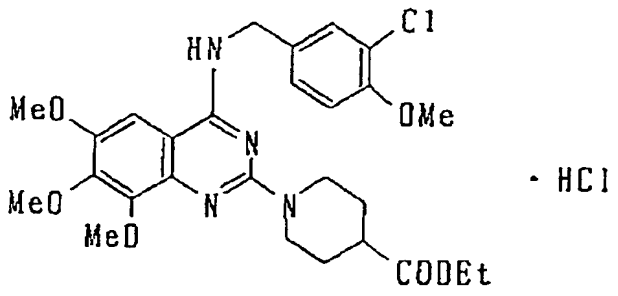


- molecular formula; $C_{27}H_{32}N_4O_7 \cdot HCl$
- yield(%); 65
- m.p.(°C); 148 ~ 150
- Mass; 525 (M + 1)

- NMR δ ($CDCl_3$);
  1.275 (3H, t, J=7.2Hz), 1.76 (2H, m), 2.03 (2H, m), 2.63 (1H, m), 3.38 (2H, m), 3.99 (3H, s), 4.08 (3H, s), 4.12 (3H, s), 4.17 (2H, q, J=7.2Hz), 4.28 (2H, m), 4.63 (2H, d, J=6.0Hz), 5.88 (2H, s), 6.68 (1H, d, J=8.0Hz), 6.92 (1H, dd, J=8.0Hz, 1.6Hz), 6.97 (1H, d, J=1.6Hz), 8.23 (1H, s), 9.38 (1H, brs), 11.1 (1H, s)

Example 211

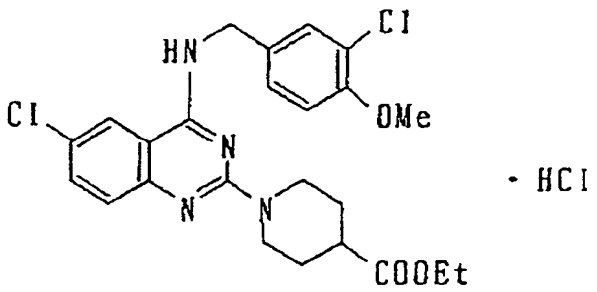
2-(4-Ethoxycarbonylpiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6,7,8-trimethoxyquinazoline hydrochloride



- molecular formula ; $C_{27}H_{33}N_4O_6Cl \cdot HCl$
- yield(%); 93
- m.p.(°C); 177 ~ 178
- Mass; 545 (M+1)
- NMR δ ($CDCl_3$);
  1.27 (3H, t, J=7.2Hz), 1.80 (2H, m), 2.06 (2H, m), 2.67 (1H, m), 3.40 (2H, m), 3.82 (3H, s), 3.98 (3H, s), 4.07 (3H, s), 4.11 (3H, s), 4.17 (2H, q, J=7.2Hz), 4.27 (2H, m), 4.65 (2H, d, J=6.0Hz), 6.84 (1H, d, J=8.8Hz), 7.40 (1H, d, J=2.0Hz), 7.48 (1H, dd, J=8.8Hz, 2.0Hz), 8.23 (1H, s), 9.26 (1H, s), 11.27 (1H, brs)

Example 212

2-(4-Ethoxycaxbonylpiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline hydrochloride

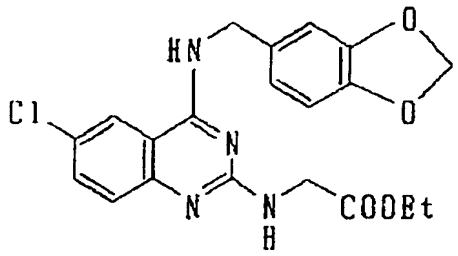


- molecular formula; $C_{24}H_{26}N_4O_3Cl_2 \cdot HCl$
- yield(%); 97
- m.p.(°C); 201 ~ 204
- Mass; 489 (M+1)
- NMR δ (DMSO-d_6);
  1.17 (3H, t, J=7.2Hz), 1.56 (2H, m), 1.93 (2H, m), 2.71 (1H, m), 3.30 (2H, m), 3.80 (3H, s), 4.06

(2H, q, J = 7.2Hz), 4.48 (2H, m), 4.66 (2H, d, J = 5.2Hz), 7.09 (1H, d, J = 8.4Hz), 7.34 (1H, dd, J = 8.4Hz, 2.0Hz), 7.49 (1H, d, J = 2.0Hz), 7.83 (2H, brs), 8.48 (1H, brs), 10.8 (1H, brs)

Example 213

2-(Ethoxycarbonylmethyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

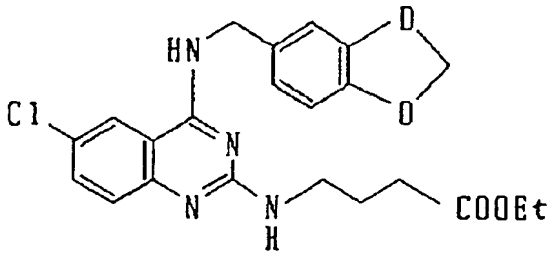


- molecular formula; $C_{20}H_{19}N_4O_4Cl$
- yield(%); 55
- m.p.(°C); 218 ~ 219 (dec.)
- Mass m/e; 415 (M + 1)
- NMR δ (DMSO-d_6);

1.13 (3H, t, J = 7.2Hz), 4.07 (2H, q, J = 7.2Hz), 4.18 (2H, brs), 4.63 (2H, brd, J = 4.0Hz), 5.97 (2H, s), 6.85 ~ 6.92 (3H, m), 7.53 (1H, brs), 7.84 (1H, brd, J = 8.0Hz), 8.35 (1H, brs), 8.50 (2H, m)

Example 214

2-(3-Ethoxycarbonylpropyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

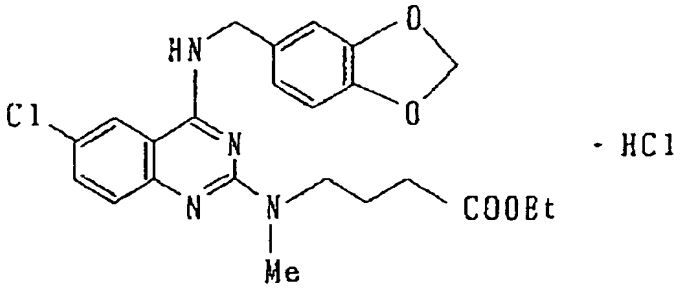


- molecular formula; $C_{22}H_{23}N_4O_4Cl$
- yield(%); 44
- m.p.(°C); 96 ~ 98
- Mass m/e; 443 (M + 1)
- NMR δ ($CDCl_3$);

1.24 (3H, t, J = 6.8Hz), 1.96 (2H, quintent, J = 7.2Hz), 2.41 (2H, t, J = 7.2Hz), 3.54 (2H, q, J = 7.2Hz), 4.12 (2H, q, J = 6.8Hz), 4.66 (2H, q, J = 5.2Hz), 5.97 (2H, s), 6.79 (1H, d, J = 8.0Hz), 6.84 (1H, d, J = 8.0Hz), 6.87 (1H, s), 7.30 (1H, d, J = 8.0Hz), 7.44 (1H, s), 7.47 (1H, d, J = 8.0Hz)

Example 215

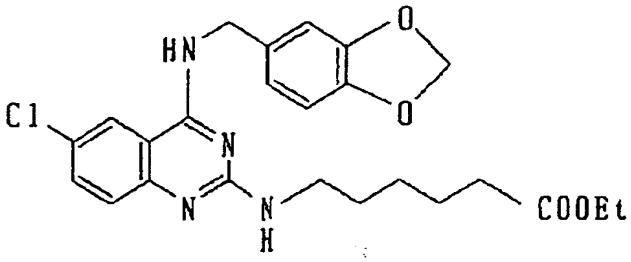
2-[N-(3-Ethoxycarbonylpropyl)-N-methylamino]-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride



- molecular formula; $C_{23}H_{25}N_4O_4Cl \cdot HCl$
- yield(%); 67
- m.p.(°C); 182 ~ 183
- Mass; 457 (M + 1)
- NMR δ ($CDCl_3$ + DMSO-d_6);
  1.23 (3H, t, J = 7.2Hz), 1.90 (2H, brs), 2.25 (2H, brs), 2.84 (3H, brs), 3.56 (2H, brs), 4.10 (2H, q, J = 7.2Hz), 4.70 (2H, d, J = 5.6Hz), 5.94 (2H, s), 6.76 (1H, d, J = 7.6Hz), 6.87 (2H, m), 7.54 (1H, dd, J = 9.2Hz, 2.0Hz), 8.40 (1H, d, J = 2.0Hz), 8.66 (1H, d, J = 9.2Hz), 9.69 (1H, brs)

Example 216

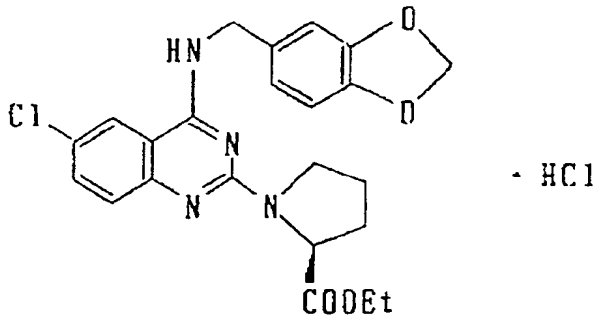
2-(5-Ethoxycarbonylpentyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{24}H_{27}N_4O_4Cl$
- yield(%); 46
- m.p.(°C); 109 ~ 110
- Mass m/e; 471 (M + 1)
- NMR δ ($CDCl_3$);
  1.25 (3H, t, J = 7.2Hz), 1.43 (2H, quintet, J = 7.6Hz), 1.66 (4H, m), 2.31 (2H, t, J = 7.6Hz), 3.49 (2H, q, J = 7.6Hz), 4.12 (2H, q, J = 7.2Hz), 4.68 (2H, d, J = 5.2Hz), 5.97 (2H, s), 6.79 (1H, d, J = 8.0Hz), 6.84 (1H, d, J = 8.0Hz), 6.87 (1H, s), 7.43 (3H, m)

Example 217

(S)-2-(N-2-Ethoxycarbonylpyrrolidin-1-yl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride

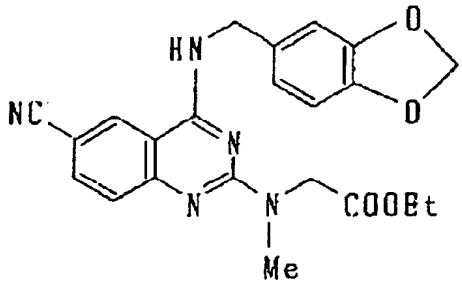


- molecular formula; $C_{23}H_{23}N_4O_4Cl \cdot HCl$
- yield(%); 52
- m.p.(°C); 206 ~ 208
- Mass; 455 (M + 1)
- NMR δ ($CDCl_3$);

  1.19 (3H, t, J = 7.2Hz), 2.17 (3H, m), 2.32 (1H, m), 4.12 (2H, m), 4.24 (2H, m), 4.62 (2H, m), 4.67 (1H, m), 5.93 (2H, s), 6.77 (1H, d, J = 8.0Hz), 6.86 (1H, dd, J = 8.0Hz, 1.6Hz), 6.89 (1H, d, J = 1.6Hz), 7.54 (1H, d, J = 8.8Hz), 8.38 (1H, s), 8.64 (1H, d, J = 8.8Hz), 9.67 (1H, brs), 13.38 (1H, brs)

Example 218

2-(N-Ethoxycarbonylmethyl-N-methylamino)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline

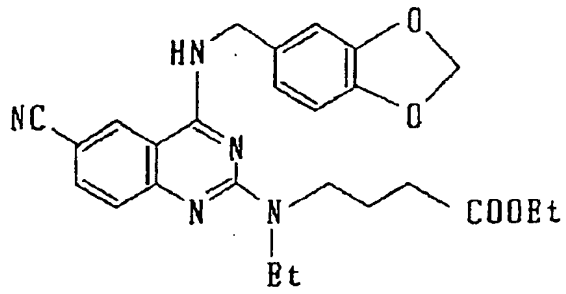


- molecular formula; $C_{22}H_{21}N_5O_4$
- yield(%); 75
- m.p.(°C); 171 ~ 172
- Mass; 420 (M + 1)
- NMR δ (DMSO-d_6);

  1.12 (3H, m), 3.18 (3H, s), 4.03 (2H, m), 4.38 (2H, m), 4.51 (2H, m), 5.95 (2H, s), 6.84 (3H, m), 7.30 (1H, m), 7.76 (1H, m), 8.58 (1H, s), 8.79 (1H, m)

Example 219

2-[N-Ethyl-N-(3-ethoxycarbonylpropyl)amino]-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline

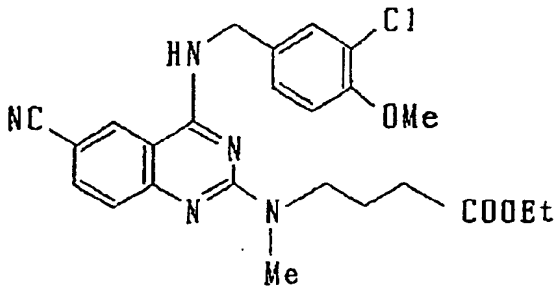


- molecular formula; $C_{25}H_{27}N_5O_4$ (461.522)
- yield(%); 61
- m.p.(°C); 142 ~ 143
- Mass; 462 (M + 1)
- NMR δ (DMSO-d_6);

  1.0 ~ 1.15 (3H, br 2 peaks), 1.13 (3H, t, J = 7.1Hz), 1.65 ~ 1.9 (2H, br 2 peaks), 2.15 ~ 2.35 (2H, br 2 peaks), 3.58 (4H, brs), 4.01 (2H, q, J = 7.1Hz), 4.58 (2H, d, J = 5.7Hz), 5.96 (2H, s), 6.84 (2H, s), 6.93 (1H, s), 7.25 (1H, brs), 7.72 (1H, dd, J = 1.8Hz, 8.8Hz), 8.56 (1H, d, J = 1.8Hz), 8.72 (1H, t, J = 5.7Hz)

Example 220

2-(N-(3-Ethoxycarbonylpropyl)-N-methylamino]-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline

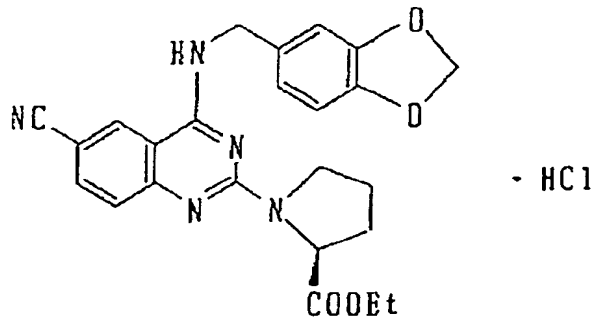


- molecular formula; $C_{24}H_{26}N_5O_3Cl$
- yield(%); 72
- m.p.(°C); 127 ~ 128
- Mass; 468 (M + 1)
- NMR δ (DMSO-d_6);

  1.11 (3H, t, J = 7.2Hz), 1.74 (2H, brs), 2.14 (2H, brs), 3.09 (3H, s), 3.62 (2H, brs), 3.81 (3H, s), 3.98 (2H, q, J = 7.2Hz), 4.61 (2H, d, J = 6.0Hz), 7.07 (1H, d, J = 8.8Hz), 7.20 ~ 7.36 (2H, m), 7.42 (1H, s), 7.72 (1H, d, J = 8.8Hz), 8.55 (1H, s), 8.75 (1H, t, J = 6.0Hz)

Example 221

(S)-2-(N-2-Ethoxycarbonylpyrrolidin-1-yl)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline hydrochloride

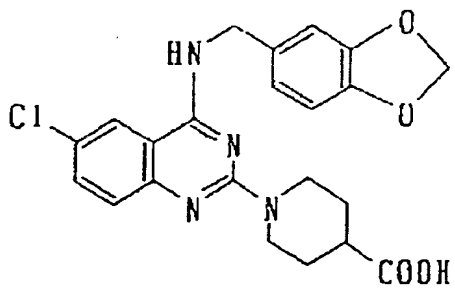


- molecular formula; $C_{24}H_{23}N_5O_4 \cdot HCl$
- yield(%); 44
- m.p.(°C); 231 ~ 232
- Mass; 446 (M + 1)
- NMR δ ($CDCl_3$);

1.21 (3H, t, J = 7.2Hz), 2.19 (3H, m), 2.36 (1H, m), 4.15 (2H, m), 4.28 (2H, m), 4.62 (2H, m), 4.76 (1H, m), 5.95 (2H, s), 6.79 (1H, d, J = 8.0Hz), 6.86 (1H, d, J = 8.0Hz), 6.88 (1H, s), 7.80 (1H, dd, J = 8.8Hz, 1.6Hz), 8.82 (1H, d, J = 1.6Hz), 8.87 (1H, d, J = 8.8Hz), 9.85 (1H, brs), 13.81 (1H, s)

Example 222

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



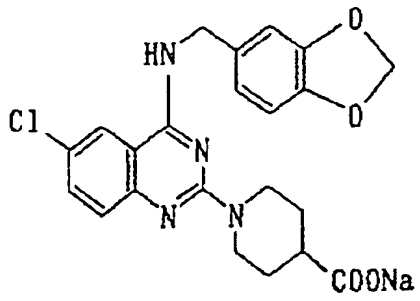
10 ml of ethanol, 5 ml of water and 820 mg of sodium hydroxide were added to 1 g of 2-(4-ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline. The obtained mixture was refluxed for 20 minutes, concentrated under a reduced pressure and neutralized with 1N hydrochloric acid. The crystals thus precipitated were recovered by filtration to give 920 mg of the title compound.

- molecular formula; $C_{22}H_{21}N_4O_4Cl$
- yield(%); 98
- m.p.(°C); 221 ~ 222
- Mass m/e; 441 (M + 1)
- NMR δ (DMSO-d_6);

1.38 (2H, m), 1.80 (2H, dd, J = 13.2Hz, 2.4Hz), 2.48 (1H, m), 2.96 (2H, t, J = 12.0Hz), 4.54 (2H, d, J = 5.6Hz), 4.56 (2H, dt, J = 12.0Hz, 3.2Hz), 5.94 (2H, s), 6.81 (1H, d, J = 8.0Hz), 6.84 (1H, d, J = 8.0Hz), 6.93 (1H, s), 7.24 (1H, d, J = 9.2Hz), 7.46 (1H, dd, J = 9.2Hz, 2.0Hz), 8.13 (1H, d, J = 2.0Hz), 8.55 (1H, t, J = 5.6Hz)

Example 223

Sodium 2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

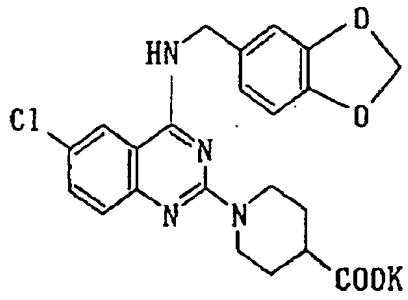


12 ml of a 1N aqueous solution of sodium hydroxide and 40 ml of water were added to 5.00 g (11.3 mmol) of the 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline prepared in Example 222. The obtained mixture was dissolved by heating and cooled by allowing to stand. The crystals thus precipitated were recovered by filtration under suction, washed with a small amount of water, and vacuum-dried in the presence of phosphorus pentaoxide to give 4.34 g of the title compound.

- molecular formula; $C_{22}H_{20}ClN_4O_4Na$
- yield(%); 98
- NMR δ (DMSO-d_6);
  1.42(2H, m), 1.73(2H, m), 2.06(1H, m), 2.95(2H, m), 4.52(2H, m), 4.56(2H, d, J=5.6Hz), 5.95(2H, s), 6.81(1H, d, J=8.0Hz), 6.86(1H, dd, J=8.0Hz, 1.6Hz), 6.95(1H, d, J=1.6Hz), 7.22(1H, d, J=9.2Hz), 7.44(1H, dd, J=9.2Hz, 2.4Hz), 8.13(1H, d, J=2.4Hz), 8.58(1H, brt, J=5.6Hz)

Example 224

Potassium 2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



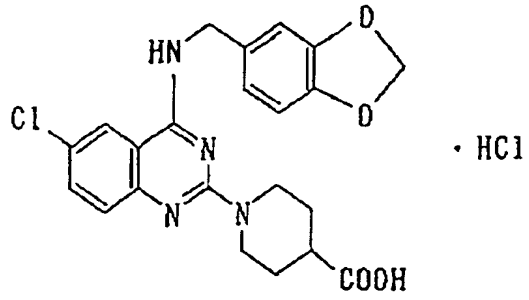
12.5 ml of a 1N aqueous solution of potassium hydroxide and 40 ml of water were added to 5.50 g (12.5 mmol) of the 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzylamino)-6-chloroquinazoline prepared in Example 222. The obtained mixture was dissolved by heating and filtered. The filtrate was concentrated in a vacuum. Ethanol and ether were added to the obtained residue to precipitate crystals. The crystals were recovered by filtration, washed with ether, and vacuum-dried in the presence of phosphorus pentaoxide to give 4.69 g of the title compound.

- molecular formula; $C_{22}H_{20}ClN_4O_4K$
- yield(%); 78
- m.p.(°C); 230 ~ 234 (dec.)
- NMR δ (DMSO-d_6);
  1.39(2H, m), 1.69(2H, m), 1.96(1H, m), 2.94(2H, m), 4.48(2H, m), 4.55(2H, d, J=5.6Hz), 5.96(2H,

s), 6.81(1H, d, J = 8.0Hz), 6.86(1H, dd, J = 8.0Hz, 1.6Hz), 6.94(1H, d, J = 1.6Hz), 7.22(1H, d, J = 8.8Hz), 7.43(1H, dd, J = 8.8Hz, 2.4Hz), 8.11(1H, d, J = 2.4Hz), 8.50(1H, brt, J = 5.6Hz)

Example 225

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride

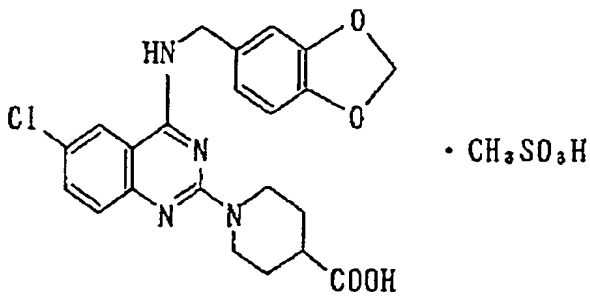


2.00 g (4.54 mmol) of the 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzylamino)-6-chloroquinazoline prepared in Example 222 was dissolved in a mixture comprising 25 ml of tetrahydrofuran and 25 ml of ethanol under heating, followed by the dropwise addition of 1.0 ml of an 8M ethanolic solution of hydrochloric acid. The obtained mixture was cooled by allowing to stand to precipitate crystals. The crystals were recovered by filtration, washed with tetrahydrofuran, and air-dried to give 1.87 g of the title compound.

- molecular formula; $C_{22}H_{21}N_4O_4Cl \cdot HCl$
- yield(%); 86
- m.p.(°C); 284 ~ 286
- NMR δ (DMSO-d_6);
  1.58(2H, m), 1.96(2H, m), 2.65(1H, m), 3.3(2H, m), 4.47(2H, m), 4.67(2H, d, J = 5.6Hz), 5.98(2H, s), 6.87(1H, d, J = 8.0Hz), 6.90(1H, dd, J = 8.0Hz, 1.6Hz), 7.00(1H, d, J = 1.6Hz), 7.83(2H, brs), 8.49(1H, brs), 10.09(1H, brs), 12.11(1H, brs), 12.40(1H, brs)

Example 226

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline methanesulfonate



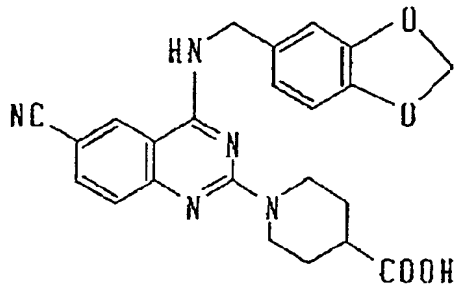
2.00 g (4.54 mmol) of the 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzylamino)-6-chloroquinazoline prepared in Example 222 was dissolved in a mixture comprising 25 ml of tetrahydrofuran and 25 ml of ethanol under heating, followed by the dropwise addition of 0.31 ml (4.78 mmol) of methanesulfonic acid. The obtained mixture was cooled by allowing to stand to precipitate crystals. The crystals were recovered by filtration, washed with tetrahydrofuran, and air-dried to give 2.21 g of the title compound.

- molecular formula; $C_{22}H_{21}N_4O_4Cl \cdot CH_4O_3S$

- yield(%); 91
- m.p.(°C); 265 ~ 266
- NMR δ (DMSO-d_6);
  1.59(2H ,m), 1.97(2H, m), 2.32(3H, s), 2.65(1H, m), 3.3(2H, m), 4.40(2H, m), 4.68(2H, d, J = 5.6Hz), 5.98(2H, s), 6.87(1H, d, J = 8.0Hz). 6.90(1H, dd, J = 8.0Hz, 1.6Hz), 6.98(1H, d, J = 1.6Hz), 7.67(1H, d, J = 8.8Hz), 7.84(1H, dd, J = 8.0Hz, 2.0Hz), 8.42(1H, d, J = 2.0Hz), 9.95(1H, brs), 11.76(1H, brs), 12.37-(1H, brs)

Example 227

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline

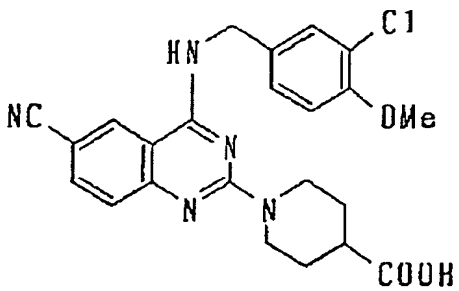


20 ml of ethanol and 2.0 ml of a 1N aqueous solution of sodium hydroxide were added to 318 mg of 2-(4-ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline. The obtained mixture was stirred at 50 °C for 30 minutes and neutralized with 1N hydrochloric acid. The crystal thus precipitated was recovered by filtration and purified by silica gel column chromatography (chloroform/methanol) to give 116 mg of the title compound.

- molecular formula; $C_{23}H_{21}N_5O_4$
- yield(%); 39
- m.p.(°C); 269 ~ 271
- Mass m/e; 432 (M + 1)
- NMR δ (DMSO-d_6);
  1.40 (2H, m), 1.79 (2H, m), 2.41 (1H, m), 3.04 (1H, dt, J = 11.2Hz, 1.2Hz), 4.55 (2H, d, J = 5.6Hz), 4.57 (2H, m), 5.95 (2H, s), 6.82 (1H, d, J = 8.0Hz), 6.84 (1H, d, J = 8.0Hz), 6.94 (1H, s), 7.25 (1H, d, J = 8.8Hz), 7.71 (1H, d, J = 8.8Hz), 8.53 (1H, s), 8.72 (1H, t, J = 5.6Hz)

Example 228

2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline



30 ml of tetrahydrofuran, 30 ml of ethanol and 14 ml of a 1N aqueous solution of sodium hydroxide were added to 1.0 g of 2-(4-ethoxycarbonylpiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-

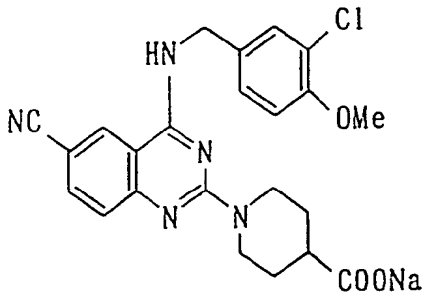
cyanoquinazoline. The obtained mixture was stirred at room temperature for 16 hours and neutralized with 1N hydrochloric acid, followed by the addition of 100 ml of water. The crystals thus precipitated were recovered by filtration and recrystallized from tetrahydrofuran/ethanol/water to give 860 mg of the title compound.

- molecular formula; $C_{23}H_{22}N_5O_3Cl$
- yield(%); 91
- m.p.(°C); 277 ~ 278 (dec.)
- Mass m/e; 452 (M + 1)
- NMR δ (DMSO-d_6);

  1.40 (2H, m), 1.84 (2H, m), 2.51 (1H, m), 3.05 (2H, dt, J = 12Hz, 2.4Hz), 3.82 (3H, s), 4.59 (2H, d, J = 5.6Hz), 4.63 (2H, m), 7.08 (1H, d, J = 8.4Hz), 7.28 (1H, d, J = 8.8Hz), 7.32 (1H, dd, J = 8.4Hz, 2.0Hz), 7.45 (1H, d, J = 2.0Hz), 7.74 (1H, dd, J = 8.8Hz, 2.0Hz), 8.54 (1H, d, J = 2.0Hz), 8.79 (1H, t, J = 5.6Hz)

Example 229

Sodium 2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline



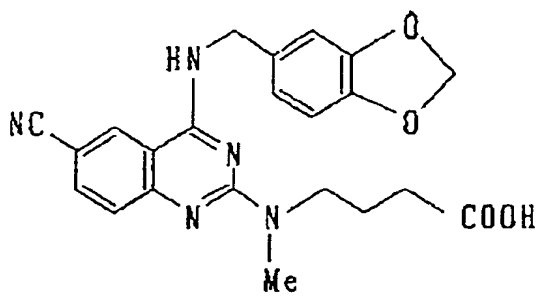
1.00 g (2.21 mmol) of the 2-(4-carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline prepared in Example 228 was dissolved in a mixture comprising 30 ml of tetrahydrofuran and 40 ml of ethanol under heating, followed by the addition of 2.3 ml of a 1N aqueous solution of sodium hydroxide and 100 ml of water. The obtained mixture was concentrated in a vacuum to precipitate crystals. The crystals were recovered by filtration, washed with water, and air-dried to give 0.45 g of the title compound.

- molecular formula; $C_{23}H_{21}N_5O_3ClNa$
- yield(%); 43
- NMR δ (DMSO-d_6);

  1.45 (2H, m), 1.75 (2H, m), 2.12 (1H, m), 3.06 (2H, m), 3.81 (3H, s), 4.52 (2H, m), 4.58 (2H, d, J = 5.6Hz), 7.07 (1H, d, J = 8.8Hz), 7.24 (1H, d, J = 8.4Hz), 7.32 (1H, dd, J = 8.4Hz, 2.0Hz), 7.45 (1H, d, J = 2.0Hz), 7.69 (1H, dd, J = 8.8Hz, 2.0Hz), 8.54 (1H, d, J = 2.0Hz), 8.86 (1H, brt, J = 5.6Hz)

Example 230

2-[N-(3-Carboxypropyl)-N-methylamino]-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



20 ml of ethanol and 2.61 ml of a 1N aqueous solution of sodium hydroxide were added to 389 mg of 2-[N-(3-ethoxycarbonylpropyl)-N-methoxyamino]-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline. The obtained mixture was stirred at room temperature for 4 hours and at 50 °C for 10 minutes and neutralized with 1N hydrochloric acid. The crystals precipitated were recovered by filtration, purified by silica gel column chromatography (chloroform/methanol) and recrystallized from ethanol/acetone/water to give 305 mg of the title compound.

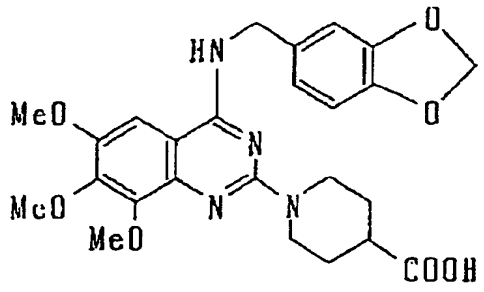
- molecular formula; $C_{22}H_{21}N_5O_4$
- yield(%); 84
- m.p.(°C); 138 ~ 140
- Mass m/e; 420 (M + 1)
- NMR δ ($CDCl_3$ (+ DMSO-d_6));
  1.96 (2H, brs), 2.31 (brs), 3.24 (3H, s), 3.76 (2H, brs), 4.67 (2H, d, J = 5.6Hz), 5.94 (2H, s), 6.77 (1H, d, J = 8.0Hz), 6.86 (1H, d, J = 8.0Hz), 6.91 (1H, s), 7.58 (1H, brs), 7.61 (1H, d, J = 8.4Hz), 8.48 (2H, m)

Examples 231 to 245

The following compounds were prepared in a similar manner to those of Examples 222 to 230.

Example 231

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6,7,8-trimethoxyquinazoline

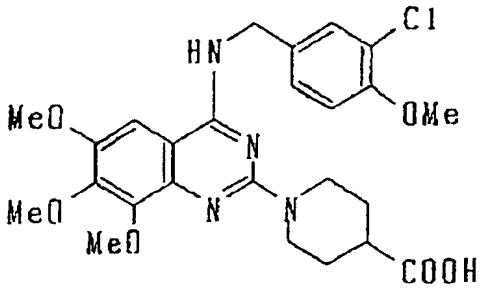


- molecular formula; $C_{25}H_{28}N_4O_7$
- yield(%); 73
- m.p.(°C); 216 ~ 217
- Mass m/e; 297 (M + 1)

- NMR δ ($CDCl_3$);
  1.80 (2H, m), 2.05 (2H, m), 2.65 (1H, m), 3.39 (2H, dt, J = 10.8Hz, 2.8Hz), 3.98 (3H, s), 4.07 (3H, s), 4.13 (3H, s), 4.26 (2H, m), 4.70 (2H, d, J = 6.0Hz), 5.88 (2H, s), 6.69 (1H, d, J = 7.6Hz), 6.95 (1H, dd, J = 7.6Hz, 1.6Hz), 7.02 (1H, d, J = 1.6Hz), 8.38 (1H, s), 9.36 (1H, s), 11.24 (1H, t, J = 6.0Hz)

Example 232

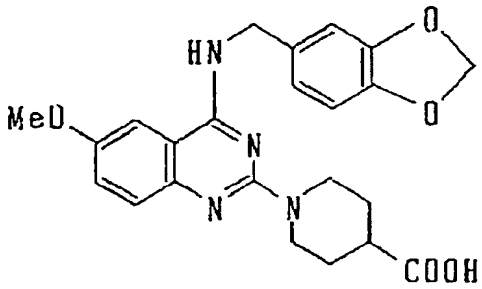
2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6,7,8-trimethoxyquinazoline



- molecular formula; $C_{25}H_{29}N_4O_6Cl$
- yield(%); 90
- m.p.(°C); 197 ~ 198
- Mass m/e; 517 (M + 1)
- NMR δ (DMSO-d_6);
  1.45 (2H, brs), 1.90 (2H, brs), 2.59 (1H, brs), 3.22 (2H, brs), 3.80 (3H, s), 3.90 (6H, s), 3.92 (3H, s), 4.39 (2H, brs), 4.65 (2H, d, J = 5.2Hz), 7.05 (1H, d, J = 8.4Hz), 7.33 (1H, d, J = 8.4Hz), 7.45 (1H, s), 7.76 (1H, brs), 10.70 (1H, brs)

Example 233

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline

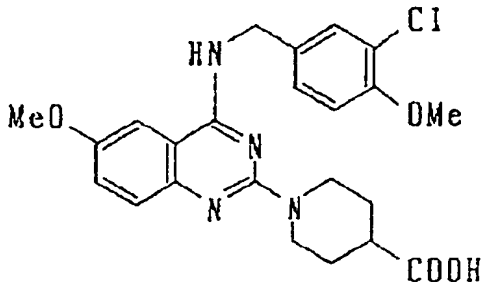


- molecular formula; $C_{23}H_{24}N_4O_5$ (436)
- yield(%); 79
- m.p.(°C); 263 (dec.)
- Mass; 437 $(M + 1)^+$
- NMR δ (DMSO-d_6);
  1.51 ~ 1.59 (2H, m), 1.86 ~ 1.95 (2H, m), 2.59 ~ 2.64 (1H, m), 3.21 ~ 3.28 (2H, m), 4.39 ~ 4.44 (2H, m), 4.67 (2H, d, J = 5.6Hz), 5.78 (2H, s), 6.85 (1H, d, J = 7.6Hz), 6.89 (1H, d, J = 7.6Hz), 6.99 (1H, s), 7.42 (1H, dd, J = 9.2Hz, 1.6Hz), 7.72 (1H, d, J = 9.2Hz), 7.86 (1H, d, J = 1.6Hz), 10.02 (1H, br), 11.89

(1H, s)

Example 234

2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-methoxyquinazoline

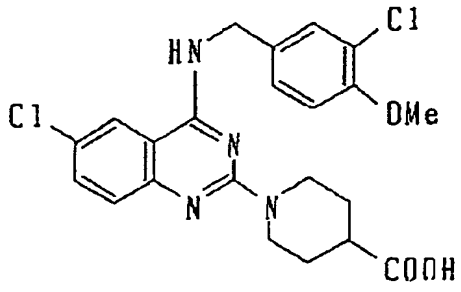


- molecular formula; $C_{23}H_{25}N_4O_4Cl$ (456.930)
- yield(%); 81
- m.p.(°C); 245 (dec.)
- Mass; 457 (MH^+)
- NMR;

1.3 ~ 1.5 (2H, m), 1.79 (2H, d, J=10Hz), 2.4 ~ 2.5 (1H, m), 2.91 (2H, t, J=11Hz), 3.81 (3H, s), 4.56 (2H, d, J=13Hz), 4.60 (2H, d, J=5.7Hz), 7.09 (1H, d, J=8.6Hz), 7.18 (1H, dd, J=2.7Hz, 9.2Hz), 7.24 (1H, d, J=9.2Hz), 7.32 (1H, dd, J=2.2Hz, 8.6Hz), 7.45 (1H, d, J=2.2Hz), 7.49 (1H, d, J=2.7Hz), 8.42 (1H, t, J=5.7Hz), 12.15 (1H, brs)

Example 235

2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinazoline

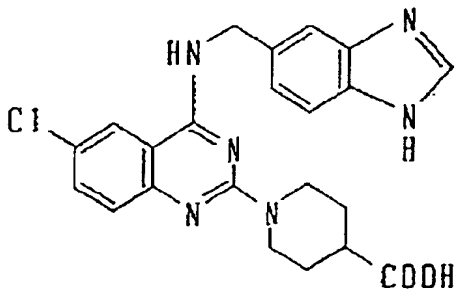


- molecular formula; $C_{22}H_{22}N_4O_3Cl_2$
- yield(%); 92
- m.p.(°C); 280 ~ 281
- Mass m/e; 461 (M+1)
- NMR δ (DMSO-d_6);

1.59 (2H, m), 1.94 (2H brd, J=11.6Hz), 2.62 (1H, brs), 3.32 (2H, m), 3.79 (3H, s), 4.52 (2H, d, J=13.6Hz), 4.64 (2H, d, J=4.8Hz), 6.99 (1H, d, J=8.4Hz), 7.30 (1H, d, J=8.4Hz), 7.42 (1H, s), 7.69 (1H, d, J=8.8Hz), 8.00 (1H, d, J=8.8Hz), 8.51 (1H, s), 10.24 (1H, s), 12.42 (1H, s)

Example 236

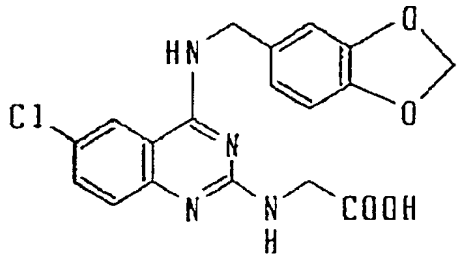
2-(4-Carboxypiperidino)-4-(benzimidazol-5-yl)methylamino-6-chloroquinazoline



- molecular formula; $C_{22}H_{21}N_6O_2Cl$ (436.903)
- yield(%); 99
- m.p.(°C); 230 (dec.)
- Mass; 437 $(MH)^+$
- NMR δ (DMSO-d_6);
  1.3 ~ 1.5 (2H, m), 1.82 (2H, d, J=10Hz), 2.4 ~ 2.5 (1H, m), 2.98 (2H, t, J=11Hz), 4.60 (2H, d, J=13Hz), 4.77 (2H, d, J=5.7Hz), 7.2 ~ 7.3 (2H, m), 7.45 ~ 7.6 (3H, m), 8.16 (1H, s), 8.19 (1H, d, J=2.4Hz), 8.68 (1H, t J=5.7Hz), 12.17 (1H, brs), 12.33 (1H, brs)

Example 237

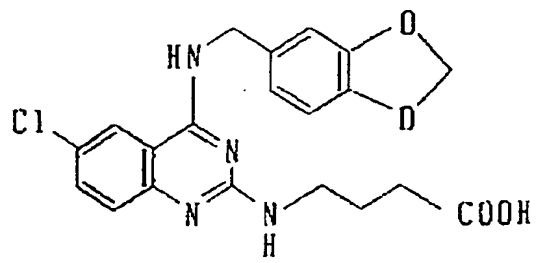
2-(Carboxymethyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{18}H_{15}N_4O_4Cl$
- yield(%); 64
- m.p.(°C); 260 ~ 261 (dec.)
- Mass m/e; 387 (M+1)
- NMR δ (DMSO-d_6);
  4.00 (2H, brs), 4.57 (2H, d, J=5.6Hz), 5.93 (2H, s), 6.79 (1H, d, J=8.0Hz), 6.86 (1H, d, J=8.0Hz), 6.95 (1H, s), 7.35 (1H, brs), 7.50 (1H, brs), 8.30 ~ 8.50 (2H, m)

Example 238

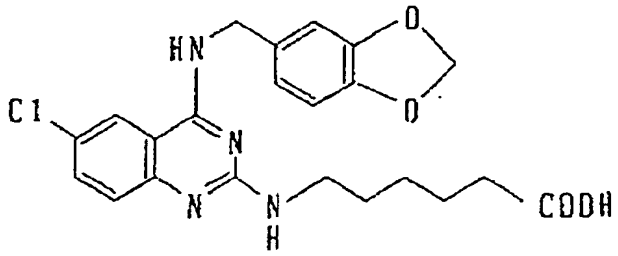
2-(3-Carboxypropyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{19}N_4O_4Cl$
- yield(%); 88
- m.p.(°C); 170 ~ 172
- Mass m/e; 415 (M+1)
- NMR δ (DMSO-d_6);
  1.71 (2H, brs), 2.23 (2H, brs), 3.27 (2H, brs), 4.56 (2H, d, J=5.6Hz), 5.95 (2H, s), 6.82 (3H, m), 6.95 (1H, s), 7.20 (1h, brs), 7.46 (1H, dd, J=8.8Hz, 1.6Hz), 8.12 (1H, d, J=1.6Hz)

Example 239

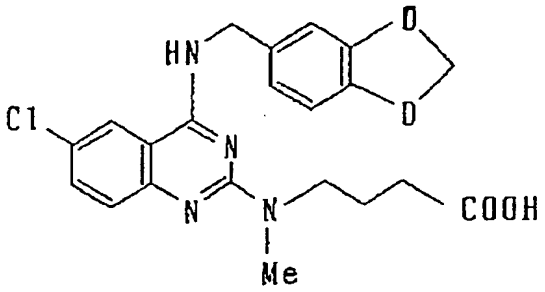
2-(5-Carboxypentyl)amino-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{22}H_{23}N_4O_4Cl$
- yield(%); 80
- m.p.(°C); 190 ~ 192
- Mass m/e; 443 (M+1)
- NMR δ (DMSO-d_6);
  1.25 (2H, brs), 1.47 (4H, brs), 2.16 (2H, brs), 3.31 (2H, brs), 4.60 (2H, brs), 5.94 (2H, s), 6.84 (2H, s), 6.96 (1H, s), 7.33 (1H, brs), 7.60 (1H, brs), 8.25 (1H, brs)

Example 240

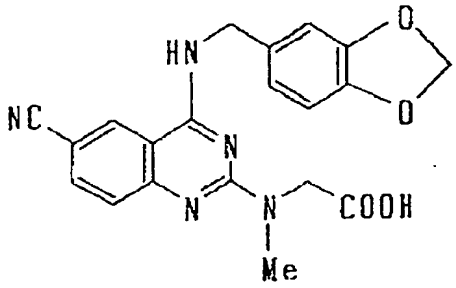
2-[N-(3-Carboxypropyl)-N-methylamino]-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{21}N_4O_4Cl$
- yield(%); 92
- m.p.(°C); 143 ~ 144
- Mass m/e; 429 (M+1)
- NMR δ (DMSO-d_6(+CD_3OD));
  1.79 (2H, brs), 2.20 (2H, brs), 3.21 (3H, s), 3.71 (2H, t, J=7.2Hz), 4.65 (2H, s), 5.95 (2H, s), 6.81 (1H, d, J=8.0Hz), 6.86 (1H, d, J=8.0Hz), 6.95 (1H, s), 7.79 (1H, d, J=8.8Hz), 7.85 (1H, d, J=8.8Hz), 8.49 (1H, s)

Example 241

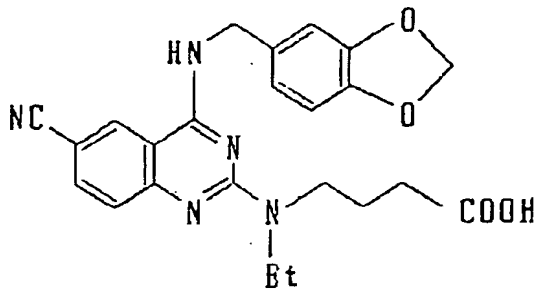
2-(N-Carboxymethyl-N-methylamino)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



- molecular formula; $C_{20}H_{17}N_5O_4$
- yield(%); 68
- m.p.(°C); 268 ~ 270
- Mass m/e; 392 (M+1)
- NMR δ (DMSO-d_6);
  3.11 (3H, s), 4.13 (2H, brs), 4.56 (2H, m), 5.94 (2H, s), 6.83 (2H, m), 6.93 (1H, d, J=14.4Hz), 7.20 (1H, m), 7.66 (1H, m), 8.51 (1H, s), 8.62 (1H, m)

Example 242

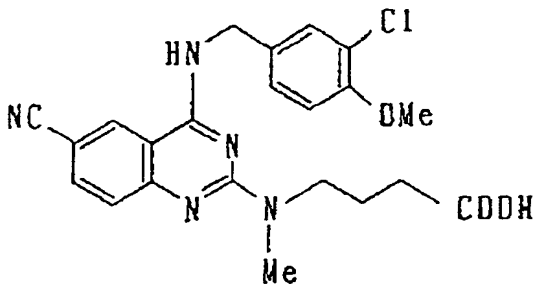
2-[N-Ethyl-N-(3-carboxypropyl)amino]-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



- molecular formula; $C_{23}H_{23}N_5O_4$ (433.468)
- yield(%); 96
- m.p.(°C); 186 ~ 187
- Mass; 434 (M + 1)
- NMR δ (DMSO-d_6);
  1.0 ~ 1.15 (3H, br 2 peaks), 1.65 ~ 1.85 (2H, br 2 peaks), 2.1 ~ 2.25 (2H, br 2 peaks), 3.57 (4H, brs), 4.58 (2H, d, J = 5.7Hz), 5.96 (2H, s), 6.84 (2H, s), 6.93 (1H, s), 7.26 (1H, d, J = 8.8Hz), 7.72 (1H, dd, J = 1.8Hz, 8.8Hz), 8.56 (1H, d, J = 1.8Hz), 8.71 (1H, brs)

Example 243

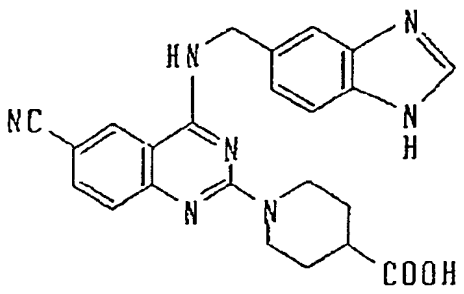
2-[N-(3-Carboxypropyl)-N-methylamino]-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinazoline



- molecular formula; $C_{22}H_{22}N_5O_3Cl$
- yield(%); 88
- m.p.(°C); 108 ~ 109
- Mass; 440 (M + 1)
- NMR δ (DMSO-d_6);
  1.73 (2H, brs), 2.13 (2H, brs), 3.11 (3H, s), 3.63 (2H, brs), 3.82 (3H, s), 4.61 (2H, d, J = 5.6Hz), 7.07 (1H, d, J = 8.4Hz), 7.27 (1H, d, J = 8.8Hz), 7.31 (1H, d, J = 8.4Hz), 7.43 (1H, s), 7.72 (1H, s), 8.55 (1H, s), 8.74 (1H, brt, J = 5.6Hz), 12.02 (1H, brs)

Example 244

2-(4-Carboxypiperidino)-4-(benzimidazol-5-yl)methylamino-6-cyanoquinazoline

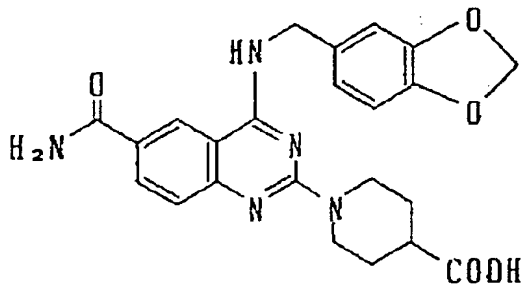


- molecular formula; $C_{23}H_{21}N_7O_2$ (427)
- yield(%); 50
- m.p.(°C); >290
- Mass; 428 ($M^+ + 1$)
- NMR δ (DMSO-d_6);

1.29 ~ 1.42 (2H, m), 1.76 ~ 2.20 (2H, m), 2.39 ~ 2.51 (2H, m), 2.99 ~ 3.07 (3H, m), 4.60 ~ 4.64 (2H, m), 4.76 (2H, d, J=5.6Hz), 7.23 (1H, d, J=8.4Hz), 7.25 (1H, d, J=8.8Hz), 7.51 (1H, d, J=8.4Hz), 7.56 (1H, s), 7.71 (1H, dd, J=8.4Hz, 1.6Hz), 8.14 (1H, s), 8.57 (1H, d, J=1.6Hz), 8.82 (1H, brt, J=5.6Hz)

Example 245

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-carbamoylquinazoline

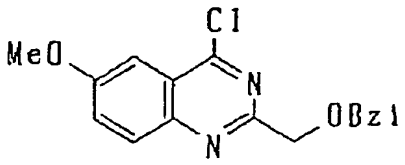


- molecular formula; $C_{23}H_{23}N_5O_5$ (449)
- yield(%); 6
- m.p.(°C); 180 ~ 182 (dec.)
- Mass; 450 (M + 1)
- NMR δ (DMSO-d_6);

1.39 (2H, m), 1.81 (2H, m), 2.48 (1H, m), 2.99 (2H, m), 4.55 (2H, d, J=5.6Hz), 4.62 (2H, m), 5.93 (2H, s), 6.81 (1H, d, J=7.6Hz), 6.85 (1H, dd, J=7.6Hz, 1.6Hz), 6.95 (1H, d, J=1.6Hz), 7.20 (1H, d, J=8.8Hz), 7.27 (1H, br), 7.71 (1H, br), 7.92 (1H, dd, J=8.8Hz, 2.0Hz), 8.57 (1H, d, J=2.0Hz), 8.59 (1H, brt, J=5.6Hz), 12.09 (1H, br)

Example 246

2-Benzyloxymethyl-4-chloro-6-methoxyquinazoline



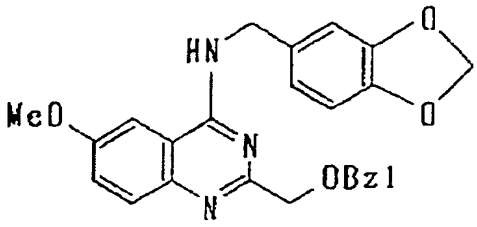
30 ml of phosphorus oxychloride was added to a suspension of 1.50 g (5.06 mmol) of 2-benzyloxymethyl-6-methoxyquinazolin-4(3H)-one in 75 ml of acetonitrile. The obtained mixture was heated under reflux. After one hour, the reaction mixture was distilled under a reduced pressure to remove the solvent and the obtained residue was dissolved in chloroform. The obtained solution was washed with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to give 1.10 g of the title compound as a yellow crystal.

- yield(%); 69
- m.p.(°C); 49 ~ 50
- Mass; 315 $(M+1)^+$
- NMR δ ($CDCl_3$);

  3.98 (3H, s), 4.79 (2H, s), 4.84 (2H, s), 7.42 (1H, d, J = 2.8Hz), 7.26 ~ 7.46 (5H, m), 7.57 (1H, dd, J = 9.2Hz, 2.8Hz), 8.01 (1H, d, J = 9.2Hz)

Example 247

2-Benzyloxymethyl-4-(3,4-methylenedioxybenzyl)amino-6-methoxyquinazoline



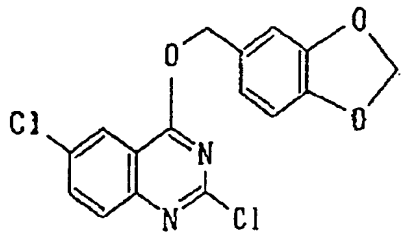
0.74 g (2.4 mmol) of the 2-benzyloxymethyl-4-chloro-6-methoxyquinazoline prepared in Example 246, 0.55 g (3.6 mmol) of piperonylamine and 0.50 g of sodium carbonate were mixed with 20 ml of isopropyl alcohol. The obtained mixture was heated under reflux. After 6 hours, the reaction mixture was distilled under a reduced pressure to remove the solvent and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) and recrystallized from chloroform/n-hexane to give 1.01 g of the title compound as a yellow crystal.

- molecular formula; $C_{25}H_{23}N_3O_4$
- yield(%); quantitative
- m.p.(°C); 158 ~ 159
- NMR δ ($CDCl_3$);

  3.91 (3H, s), 4.69 (2H, s), 4.77 (2H, s), 4.79 (2H, d, J = 5.6Hz), 5.94 (2H, s), 6.77 (1H, d, J = 7.6Hz), 6.90 (1H, dd, J = 7.6Hz, 1.6Hz), 6.94 (1H, d, J = 1.6Hz), 7.10 (1H, brs), 7.25 ~ 7.35 (5H, m), 7.41 ~ 7.44 (2H, m), 7.81 (1H, d, J = 9.2Hz)

Example 248

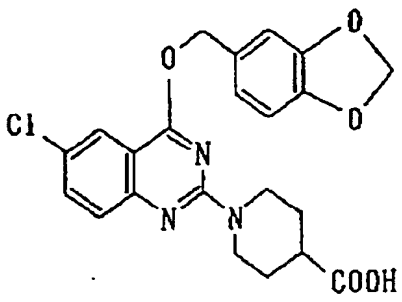
2,6-Dichloro-4-(3,4-methylenedioxybenzyl)oxyquinazoline



- molecular formula; $C_{16}H_{10}Cl_2N_2O_3$
- yield(%); 55
- m.p.(°C); 141 ~ 142
- Mass m/e; 349 (M+1)
- NMR δ ($CDCl_3$);
  5.54(2H, s), 6.01(2H, s), 6.86(1H, d, J=8.8Hz), 7.01(1H, d, J=8.8Hz), 7.02(1H, s), 7.76(1H, dd, J=8.0Hz, 2.4Hz), 7.81(1H, dd, J=8.0Hz, 0.8Hz), 8.09(1H, dd, J=2.4Hz, 0.8Hz)

Example 249

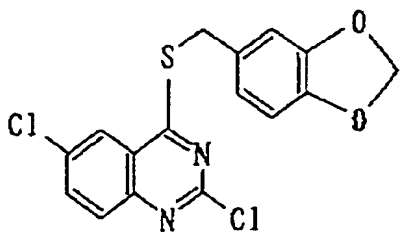
2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)oxy-6-chloroquinazoline



- molecular formula; $C_{22}H_{20}ClN_3O_5$
- yield(%); 84
- m.p.(°C); 145 ~ 147
- Mass m/e; 442 (M+1)
- NMR δ (DMSO-d_6) ;
  1.47(2H, m), 1.88(2H, m), 2.49(1H, m), 3.10(2H, brt, J=13.2Hz), 4.60(2H, brd, J=13.2Hz), 5.43-(2H, s), 6.01(2H, s), 6.91(1H, d, J=8.0Hz), 7.02(1H, d, J=8.0Hz), 7.11(1H, s), 7.39(1H, d, J=8.8Hz), 7.61(1H, dd, J=8.8Hz, 2.4Hz), 7.77(1H, d, J=2.4Hz)

Example 250

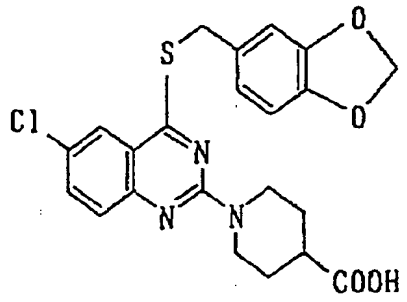
2,6-Dichloro-4-(3,4-methylenedioxybenzyl)thioquinazoline



- molecular formula; $C_{16}H_{10}Cl_2N_2O_2S$
- yield(%); 92
- m.p.(°C); 180 ~ 182
- Mass m/e; 365 (M + 1)
- NMR δ ($CDCl_3$);
  4.55 (2H, s), 5.96 (2H, s), 6.77 (1H, d, J = 8.4Hz), 6.96 (1H, s), 6.96 (1H, d, J = 8.4Hz), 7.77 (1H, dd, J = 8.8Hz, 2.0Hz), 7.82 (1H, d, J = 8.8Hz), 7.99 (1H, dd, J = 2.0Hz)

Example 251

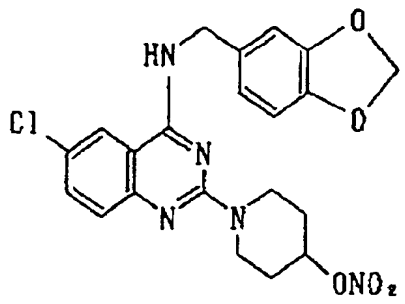
2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)thio-6-chloroquinazoline



- molecular formula; $C_{22}H_{20}ClN_3O_4S$
- yield(%); 98
- m.p.(°C); 153 ~ 154
- Mass m/e; 458 (M + 1)
- NMR δ (DMSO-d_6);
  1.50(2H, m), 1.82(2H, m), 2.39(1H, brs), 3.18(2H, m), 4.48(2H, s), 4.55(2H, brs), 5.96(2H, s), 6.82-(1H, d, J = 8.0Hz), 6.92(1H, d, J = 8.0Hz), 6.99(1H, s), 7.41(1H, brd, J = 8.8Hz), 7.62(1H, brd, J = 8.8Hz), 7.69(1H, brs)

Example 252

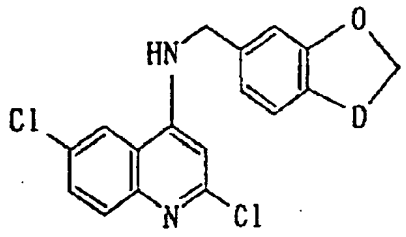
2-(4-Nitroxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{20}ClN_5O5$
- yield(%); 11
- m.p.(°C); oily substance
- Mass m/e; 458 (MH^+)
- NMR δ ($CDCl_3$);
  1.71~1.82(2H, m), 2.02~2.10(2H, m), 3.56~3.63(2H, m), 4.39~4.44(2H, m), 4.66(2H, d, J=5.2Hz), 5.18~5.22(1H, m), 5.61(1H, brt, J=5.2Hz), 5.96(2H, s), 6.79(1H, d, J=7.6Hz), 6.84(1H, dd, J=7.6Hz, 1.2Hz), 6.87(1H, d, J=1.2Hz), 7.39(1H, d, J=8.8Hz), 7.43~7.47(2H, m)

Example 253

2,6-Dichloro-4-(3,4-methylenedioxybenzyl)aminoquinoline



a) 2,4,6-Trichloroquinoline

The title compound was prepared from methyl 5-chloroanthranilate in a similar manner to that described in Journal of American Chemical Society, 68, 1285 (1946).

- NMR δ ($CDCl_3$);
  7.55(1H, s), 7.74(1H, dd, J=9.0Hz, 2.2Hz), 7.98(1H, d, J=9.0Hz), 8.19(1H, d, J=2.2Hz)

b) 2,6-Dichloro-4-(3,4-methylenedioxybenzyl)aminoquinoline

A reaction of a mixture comprising 500 mg of the compound prepared in the step (a), 350 mg of 3,4-methylenedioxybenzylamine, 1 ml of N,N-diisopropylethylamine and 4 ml of N-methyl-2-pyrrolidone was conducted on an oil bath of 130°C for 10 hours. Water was added to the reaction mixture and the obtained mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was subjected to column chromatography with 5 to 20% ethyl acetate/hexane to give 430 mg of the title compound as a highly polar component.

- molecular formula; $C_{17}H_{12}Cl_2N_2O_3$
- m.p.(°C); 198 ~ 199
- Mass m/e; 347 (M + 1)
- NMR δ ($CDCl_3$) ;

4.39(2H, d, J = 4.9Hz), 5.21(1H, t, J = 4.9Hz), 6.00(2H, s), 6.47(1H, s), 6.82~6.87(3H, m), 7.58(1H, dd, J = 9.0Hz, 2.2Hz), 7.65(1H, d, J = 2.2Hz), 7.84(1H, d, J = 9.0Hz)

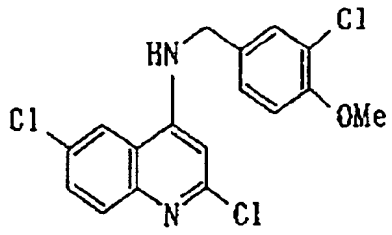
Simultaneously, 190 mg of 4,6-dichloro-2-(3,4-methylenedioxybenzyl)aminoquinoline was obtained as a lowly polar component.

- NMR δ ($CDCl_3$);

4.58(2H, d, J = 5.7Hz), 5.00(1H, brt, J = 5.7Hz), 5.94(2H, s), 6.74(1H, s), 6.77(1H, d, J = 7.9Hz), 6.84(1H, dd, J = 7.9Hz, 1.6Hz), 6.88(1H, d, J = 1.6Hz), 7.50(1H, dd, J = 9.0Hz, 2.4Hz), 7.62(1H, d, J = 9.0Hz), 7.96(1H, d, J = 2.4Hz)

Example 254

2,6-Dichloro-4-(3-chloro-4-methoxybenzylamino)quinoline



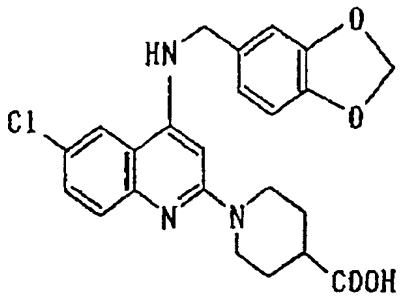
The titled compound was prepared in a similar manner to that of Example 253.

- molecular formula; $C_{17}H_{13}Cl_3N_2O$
- yield(%); 59
- m.p.(°C); 204 ~ 205
- NMR δ ($CDCl_3$) ;

3.91(3H, s), 3.40(3H, s), 4.38(2H, d, J = 5.1Hz), 4.97(1H, t, J = 5.1Hz), 5.93(1H, s), 6.93(1H, d, J = 8.4Hz), 7.24(1H, dd, J = 8.4Hz, 2.2Hz), 7.40(1H, d, J = 2.2Hz), 7.50(1H, dd, J = 8.8Hz, 2.2Hz), 7.59-(1H, d, J = 2.2Hz), 7.71(1H, d, J = 8.8Hz)

Example 255

2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinoline



a) 2-(4-Ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinoline

A reaction of a mixture comprising 130 mg of 2,6-dichloro-4-(3,4-methylenedioxybenzyl)aminoquinoline, 500 μl of ethyl isonipecotate and 1 ml of N-methyl-2-pyrrolidone was conduct on an oil bath at 150 °C for 3 hours. The reaction mixture was cooled, followed by the addition of water. The resulting mixture was extracted with ethyl acetate and the ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 20 to 50% ethyl acetate/hexane to give 150 mg of the title compound.

- NMR δ ($CDCl_3$) ;
  1.26(3H, t, J=7.1Hz), 1.70~1.81(2H, m), 1.95~2.02(2H, m), 2.54(1H, tt, J=11.2Hz, 3.8Hz), 2.97~3.06(2H, m), 4.14(2H, q, J=7.1Hz), 4.32~4.39(4H, m), 4.86(1H, t, J=5.5Hz), 5.98(3H, s), 6.81(1H, d, J=7.7Hz), 6.84~6.89(2H, m), 7.39(1H, dd, J=9.0Hz, 2.4Hz), 7.47(1H, d, J=2.4Hz), 7.55(1H, d, J=9.0Hz)

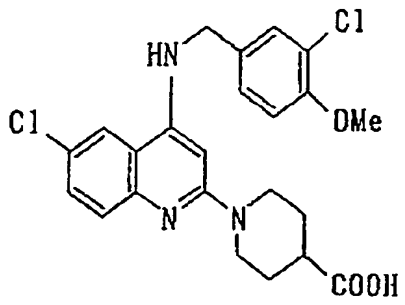
b) 2-(4-Carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinoline

A reaction of a mixture comprising 150 mg of the compound prepared in the step (a), 1 ml of a 1N aqueous solution of sodium hydroxide and 10 ml of ethanol was conducted on an oil bath at 60 °C for 2 hours. The reaction mixture was concentrated, followed by the addition of water. The resulting mixture was neutralized by the addition of 1 ml of 1N hydrochloric acid to precipitate crystals. The crystals were recovered by filtration, washed with water, and dried to give 130 mg of the title compound.

- molecular formula; $C_{23}H_{22}ClN_3O_4$
- yield(%); 92
- m.p.(°C); 235 ~ 237
- Mass m/e; 440 (M+1)
- NMR δ (DMSO-d_6) ;
  1.37~1.50(2H, m), 1.77~1.86(2H, m), 2.89~3.00(2H, br, 3 peak), 4.20~4.28(2H, br, 2 peak), 4.42-(2H, d, J=5.7Hz), 5.96(2H, s), 5.97(1H, s), 6.85(1H, d, J=7.9Hz), 6.92(1H, dd, J=7.9Hz, 1.5Hz), 6.98-(1H, d, J=1.5Hz), 7.42(2H, brs), 7.58(1H, brs), 8.15(1H, brs)

Example 256

2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinoline



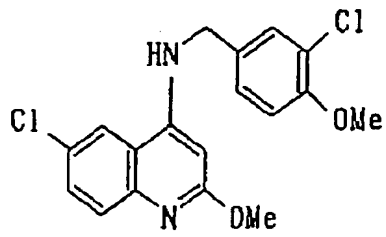
The title compound was prepared in a similar manner to that of Example 255.

- molecular formula; $C_{23}H_{23}Cl_2N_3O_3$
- m.p.(°C); 282 ~ 283
- Mass m/e; 460 (M + 1)
- NMR δ (DMSO-d_6) ;

  1.36~1.48(2H, m), 1.76~1.84(2H, m), 2.43~2.53(1H, m), 2.91(2H, t, J = 11.2Hz), 4.26(2H, brd, J = 13.2Hz), 4.44(2H, d, J = 5.9Hz), 5.97(1H, s), 7.10(1H, d, J = 8.6Hz), 7.36(1H, dd, J = 8.6Hz, 2.2Hz), 7.38(2H, s), 7.50(2H, brs and d, J = 2.2Hz), 8.11(1H, s)

Example 257

2-Methoxy-4-(3-chloro-4-methoxybenzyl)amino-6-chloroquinoline



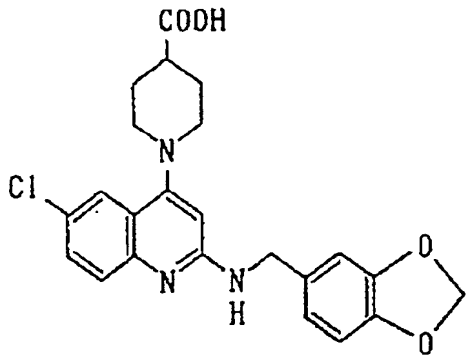
A mixture comprising 200 mg of 2,6-dichloro-4-(3-chloro-4-methoxybenzyl)aminoquinoline, 0.5 ml of methanol, 200 mg of potassium t-butoxide and 3 ml of 1,4-dioxane was heated under reflux for one hour and cooled, followed by the addition of water. The resulting mixture was extracted with ethyl acetate and the ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 10 to 30% ethyl acetate/hexane and recrystallized from ethyl acetate/hexane to give 150 mg of the title compound.

- molecular formula; $C_{18}H_{16}Cl_2N_2O_2$
- yield(%); 76
- m.p.(°C); 170 ~ 171
- NMR δ ($CDCl_3$) ;

  3.93(3H, s), 4.42(2H, d, J = 5.2Hz), 5.22(1H, t, J = 5.2Hz), 6.46(1H, s), 6.96(1H, d, J = 8.4Hz), 7.25-(1H, dd, J = 8.4Hz, 2.2Hz), 7.41(1H, d, J = 2.2Hz), 7.59(1H, dd, J = 9.0Hz, 2.2Hz), 7.66(1H, d, J = 2.2Hz), 7.85(1H, d, J = 9.0Hz)

Example 258

2-(3,4-Methylenedioxybenzylamino)-4-(4-carboxypiperidino)-6-chloroquinoline

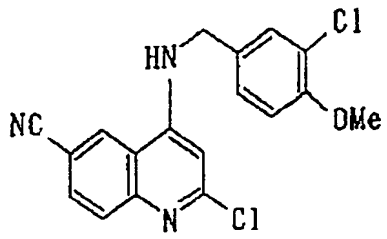


130 mg of the title compound was prepared from 140 mg of the 4,6-dichloro-2-(3,4-methylenedioxybenzyl)aminoquinoline prepared in the step (b) of Example 253 as a by-product in a similar manner to that of Example 255.

- molecular formula; $C_{23}H_{22}ClN_3O_4$
- yield(%); 99
- m.p.(°C); 270 ~ 272
- Mass m/e; 440 (M + 1)
- NMR δ (DMSO-d_6) ;
  1.78~1.89(2H, m), 1.96~2.04(2H, m), 2.70~2.79(2H, m), 3.26~3.36(2H, m), 4.49(2H, d, J = 5.7Hz), 5.96(2H, s), 6.37(1H, s), 6.85(2H, s), 6.94(1H, s), 7.37(1H, t, J = 5.7Hz), 7.41(1H, dd, J = 8.8Hz, 2.4Hz), 7.46(1H, d, J = 8.8Hz), 7.60(1H, d, J = 2.4Hz)

Example 259

2-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinoline



a) 4-Hydroxyquinolin-2-one-6-carboxylic acid

The title compound was prepared from dimethyl 4-aminobenzene-1,4-dicarboxylate in a similar manner to that described in Journal of American Chemical Society, 68, 1285 (1946).

- NMR δ (DMSO-d_6) ;
  5.79(1H, s), 7.31(1H, d, J = 8.6Hz), 8.02(1H, dd, J = 8.6Hz, 2.0Hz), 8.39(1H, d, J = 2.0Hz), 11.51(1H, s), 11.63(1H, brs), 12.86(1H, brs)

b) 2,4-Dichloroquinoline-6-carboxamide

A mixture comprising 9 g of the compound prepared in the step (a) and 50 ml of phosphorus oxychloride was heated under reflux for one hour. The reaction mixture was concentrated and ethyl acetate/acetone was added to the obtained residue to form a homogeneous suspension. This suspension was gradually poured into concentrated aqueous ammonia cooled with ice under stirring. After 30 minutes, the crystals thus precipitated were recovered by filtration, washed with water and ethyl acetate, and dried to give 8.96 g of the title compound.

- NMR δ (DMSO-d_6) ;
  7.72(1H, brs), 8.06(1H, s), 8.10(1H, d, J=8.8Hz), 8.34(1H, dd, J=8.8Hz, 2.0Hz), 8.43(1H, brs), 8.73(1H, d, J=2.0Hz)

c) 2,4-Dichloro-6-cyanoquinoline

A mixture comprising 3 g of the compound prepared in the step (b), 300 mg of lithium chloride and 30 ml of phosphorus oxychloride was heated under reflux for 2 hours. The reaction mixture was concentrated, followed by the addition of 120 ml of benzene. The resulting mixture was washed with a saturated aqueous solution of sodium hydrogencarbonate. The benzene layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and filtered through a silica gel bed. The silica gel was further washed with benzene. The benzene solutions were combined and concentrated and the residue was recrystallized from ethyl acetate/hexane to give 2.15 g of the title compound.

- NMR δ ($CDCl_3$) ;
  7.65(1H, s), 7.95(1H, dd, J=8.8Hz, 1.8Hz), 8.14(1H, d, J=8.8Hz), 8.60(1H, d, J=1.8Hz)

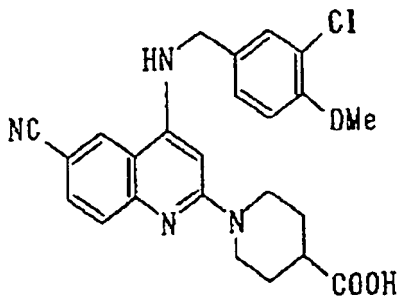
d) 2-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinoline

A reaction of a mixture comprising 1 g of the compound prepared in the step (c), 1 g of 3-chloro-4-methoxybenzylamine hydrochloride, 2.4 ml of N,N-diisopropylethylamine and 10 ml of N-methyl-2-pyrrolidone was conducted on an oil bath at 130 °C for one hour. The reaction mixture was cooled, followed by the addition of water and ethyl acetate. The crystals thus precipitated were recovered by filtration, washed with water and ethyl acetate, and dried to give 610 mg of the title compound.

- molecular formula; $C_{18}H_{13}Cl_2N_3O$
- yield(%); 38
- m.p.(°C); 254 ~ 255
- NMR δ ($CDCl_3$) ;
  3.94(3H, s), 4.45(2H, d, J=4.9Hz), 5.41(1H, d, J=4.9Hz), 6.54(1H, s), 6.98(1H, d, J=8.4Hz), 7.26-(1H, dd, J=8.4Hz, 2.2Hz), 7.41(1H, d, J=2.2Hz), 7.80(1H, dd, J=8.8Hz, 1.6Hz), 7.97(1H, d, J=8.8Hz), 8.08(1H, d, J=1.6Hz)

Example 260

2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinoline



a) 2-(4-Ethoxycarbonylpiperidino)-4-(3-chloro-4-methoxybenzylamino)-6-cyanoquinoline

A mixture comprising 750 mg of 2-chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanoquinoline, 1.6 ml of isonipecotic acid and 5 ml of N-methyl-2-pyrrolidone was heated on an oil bath at 130 °C for 3 hours and cooled, followed by the addition of water. The resulting mixture was extracted with ethyl acetate and the ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was subjected to silica gel column chromatography (20 to 40% ethyl acetate/hexane) and thereafter recrystallized from ethyl acetate/hexane to give 860 mg of the title compound.

- NMR δ ($CDCl_3$) ;
  1.26(3H, t, J=7.1Hz), 1.68~1.79(2H, m), 1.95~2.03(2H, m), 2.58(1H, tt, J=11.0Hz, 4.0Hz), 3.03~3.12(2H, m), 3.92(3H, s), 4.15(2H, q, J=7.1Hz), 4.36~4.43(4H, m), 5.08(1H, t, J=5.1Hz), 5.94(1H, s), 6.95(1H, d, J=8.4Hz), 7.26(1H, dd, J=8.4Hz, 2.2Hz), 7.42(1H, d, J=2.2Hz), 7.55~7.61(2H, m), 7.88(1H, s)

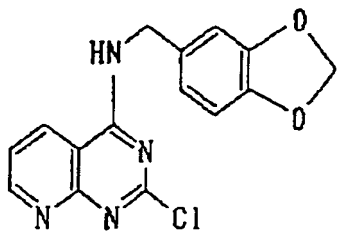
b) 2-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzylamino)-6-cyanoquinoline

A mixture comprising 500 mg of the compound prepared in the step (a), 2 ml of a 1N aqueous solution of sodium hydroxide, 20 ml of tetrahydrofuran and 25 ml of ethanol was reacted at 50 °C for 2 hours, followed by the addition of 2 ml of 1N hydrochloric acid. About 20 ml of the solvents was distilled away to precipitate crystals. The crystals were recovered by filtration, washed with water and ethyl acetate, and dried to give 460 mg of the title compound.

- molecular formula; $C_{24}H_{23}ClN_4O_3$
- yield(%); 98
- m.p.(°C); 274 ~ 276 (dec.)
- NMR δ (DMSO-d_6) ;
  1.35~1.47(2H, m), 1.78~1.87(2H, m), 2.47~2.56(1H, m), 2.95~3.04(2H, m), 3.81(3H, s), 4.30~4.39(2H, m), 4.46(2H, d, J=5.7Hz), 6.01(1H, s), 7.11(1H, d, J=8.6Hz), 7.37(1H, dd, J=8.6Hz, 2.2Hz), 7.40(1H, d, J=8.8Hz), 7.52(1H, d, J=2.2Hz), 7.65(1H, dd, J=8.8Hz, 1.6Hz), 7.68(1H, t, J=5.7Hz), 8.55(1H, d, J=1.6Hz), 12.20(1H, brs)

Example 261

2-Chloro-8-(3,4-methoxydioxybenzyl)aminopyrido[2,3-d]pyrimidine



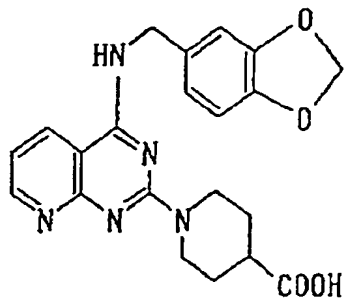
66 mg of triethylamine and 89 mg of piperonylamine were added to a solution of 118 mg of 2,8-dichloropyrido[2,3-d]pyrimidine in 20 ml of tetrahydrofuran. The obtained mixture was stirred at room temperature for 16 hours, followed by the addition of water. The crystals thus precipitated were recovered by filtration, whereby 166 mg of the title compound was obtained.

- molecular formula; $C_{15}H_{11}ClN_4O_2$
- yield(%); 89
- m.p.(°C); 200 ~ 202
- Mass m/e; 315 (M + 1)
- NMR δ (DMSO-d_6) ;

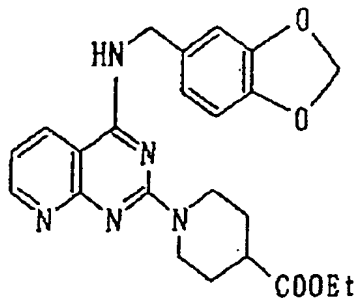
  4.64(1H, d, J = 5.6Hz), 5.97(2H, s), 6.85(1H, d, J = 8.0Hz), 6.87(1H, d, J = 8.0Hz), 6.96(1H, s), 7.55-(1H, dd, J = 8.0Hz, 4.4Hz), 8.73(1H, dd, J = 8.0Hz, 1.6Hz), 8.96(1H, dd, J = 4.4Hz, 1.6Hz), 9.46(1H, t, J = 5.6Hz)

Example 262

2-(4-Carboxypiperidino)-8-(3,4-methylenedioxybenzyl)aminopyrido[2,3-d]pyrimidine

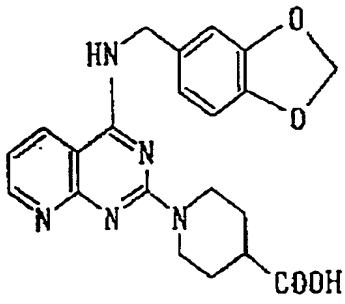


a) 2-(4-ethoxycarbonylpiperidino)-8-(3,4-methylenedioxybenzylamino)pyrido[2,3-d]pyrimidine



41 mg of triethylamine add 190 mg of ethyl isonipecotate were added to a solution of 127 mg of 2-chloro-8-(3,4-methylenedioxybenzyl)aminopyrido[2,3-d]pyrimidine in 8 ml of tetrahydrofuran. The obtained mixture was refluxed for 2 hours, followed by the addition of water. The resulting mixture was extracted with chloroform twice. The organic layers were combined, dried over magnesium sulfate, and distilled to remove the solvent. The residue was purified by silica gel chromatography (with ethyl acetate) to give 175 mg of the title compound (in a yield of 100%).

b) 2-(4-carboxypiperidino)-8-(3,4-methylenedioxybenzyl)aminopyrido[2,3-d]pyrimidine



1.56 ml of 1N sodium hydroxide was added to a solution of 170 mg of 2-(4-ethoxycarbonylpiperidino)-8-(3,4-methylenedioxybenzyl)aminopyrido[2,3-d]pyrimidine in 10 ml of ethanol. The obtained mixture was stirred at room temperature for 6 hours and neutralized by the addition of 1N hydrochloric acid and water.

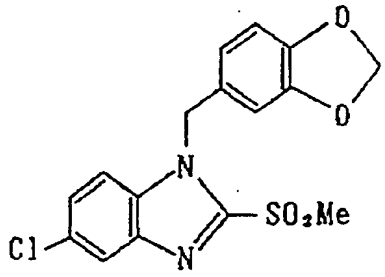
The crystals thus precipitated were recovered by filtration, whereby 121 mg of the title compound was obtained.

- molecular formula; $C_{21}H_{21}N_5O_4$
- yield(%); 76
- m.p.(°C); 255 ~ 256
- Mass m/e; 408 (M + 1)
- NMR δ (DMSO-d_6) ;

  1.39(2H, m), 1.80(2H, m), 2.51(1H, m), 3.01(2H, brt, J = 11.2Hz), 4.56(2H, d, J = 5.6Hz), 4.61(2H, brd, J = 12.8Hz), 5.94(2H, s), 6.82(1H, d, J = 8.0Hz), 6.84(1H, d, J = 8.0Hz), 6.93(1H, s), 7.03(1H, dd, J = 8.0Hz, 4.4Hz), 8.38(1H, dd, J = 8.0Hz, 1.6Hz), 8.61(1H, dd, J = 4.4Hz, 1.6Hz), 8.70(1H, t, J = 5.6Hz), 12.16(1H, brs)

Example 263

5-Chloro-2-methanesulfonyl-1-(3,4-methylenedioxybenzyl)benzimidazole



8.89 g of 6-chloro-2-mercaptobenzimidazole was dissolved in 150 ml of dimethylformamide, followed by the addition of 6.65 g of potassium carbonate and 6.15 g of methyl iodide under cooling with ice. The obtained mixture was stirred at that temperature for 50 minutes, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated in a vacuum to give crude 6-chloro-2-methylthiobenzimidazole.

This crude product was dissolved in 100 ml of methylene chloride, followed by the addition of 17.3 g of 80% m-CPBA under cooling with ice. The obtained mixture was stirred at room temperature overnight, followed by the addition of 7 g of sodium thiosulfate. The resulting mixture was stirred at room temperature for 30 minutes, followed by the addition of water. The organic layer was recovered, dried and subjected to silica gel column chromatography to give 10 g of 6-chloro-2-methanesulfonylbenzimidazole.

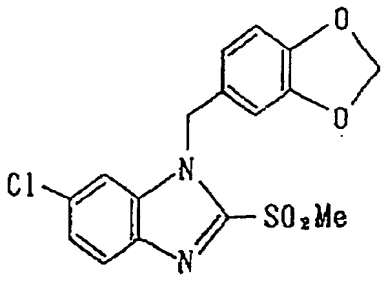
2.3 g of the 6-chloro-2-methanesulfonylbenzimidazole was dissolved in 30 ml of dimethylformamide, followed by the addition of 480 mg of 60% sodium hydride and 2.04 g of piperonyl chloride under cooling with ice. The obtained mixture was maintained at 80 °C by heating for 4 hours, allowed to stand overnight and filtered to remove insolubles. The filtrate was concentrated in a vacuum and subjected to silica gel column chromatography to give the title compound.

- molecular formula; $C_{16}H_{13}ClN_2O_4S$
- yield(%); 25
- m.p.(°C); 129 ~ 131
- Mass m/e; 365 (MH^+)
- NMR δ ($CDCl_3$) ;

  3.48(3H, s), 5.64(2H, s), 5.91(2H, s), 6.73~6.76(3H, m), 7.27(1H, d, J = 8.8Hz), 7.31(1H, dd, J = 8.8Hz, 2.0Hz), 7.80(1H, d, J = 2.0Hz)

Example 264

6-Chloro-2-methanesulfonyl-1-(3,4-methylenedixoybenzyl)benzimidazole



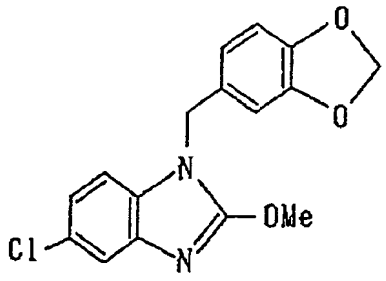
The title compound was obtained by further elution after the elution of the 5-chloro-2-methanesulfonyl-1-(3,4-methylene-dixoybenzyl) benzimidazole in Example 263.

- molecular formula; $C_{16}H_{13}ClN_2O_4S$
- yield(%); 22
- m.p.(°C); 140 ~ 142
- Mass m/e; 365 (MH^+)
- NMR δ ($CDCl_3$) ;

  3.48(3H, s), 5.62(2H, s), 5.93(2H, s), 6.73~6.77(3H, m), 7.32(1H, d, J=8.4Hz), 7.33(1H, d, J=1.2Hz), 7.74(1H, dd, J=8.4Hz, 1.2Hz)

Example 265

5-Chloro-2-methoxy-1-(3,4-methylenedioxybenzyl)benzimidazole



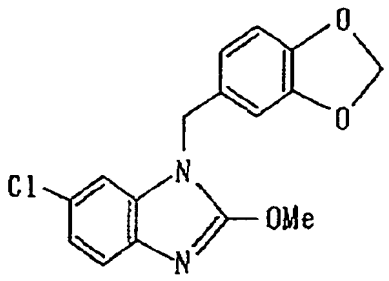
448 mg of a mixture comprising 5-chloro-2-sulfonylmethyl-1-(3,4-methylenedioxybenzyl)benzimidazole and 6-chloro-2-sulfonylmethyl-1-(3,4-methylenedioxybenzyl)benzimidazolewas dissolved in 20 ml of methanol, followed by the addition of 10 ml of 28% sodium methoxide. The obtained mixture was heated under reflux for 1.5 hours, cooled with ice, neutralized with 10% aqueous hydrochlic acid, and extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated in a vacuum. The residue was subjected to silica gel column chromatography to give the title compound.

- molecular formula; $C_{16}H_{13}ClN_2O_3$
- yield(%); 31
- m.p.(°C); 117 ~ 118
- Mass m/e; 317 (MH^+)
- NMR δ ($CDCl_3$) ;

  4.21(3H, s), 5.01(2H, s), 5.92(2H, s), 6.65(1H, d, J=1.6Hz), 6.68(1H, dd, J=8.0Hz, 1.6Hz), 6.73-(1H, d, J=8.0Hz), 6.96(1H, d, J=8.4Hz), 7.05(1H, dd, J=8.4Hz, 2.0Hz), 7.51(1H, d, J=2.0Hz)

Example 266

6-Chloro-2-methoxy-1-(3,4-methylenedioxybenzyl)benzimidazole



The title compound was obtained by further elution after the elution of the 5-chloro-2-methoxy-1-(3,4-methylenedioxybenzyl)benzimidazole in Example 265.

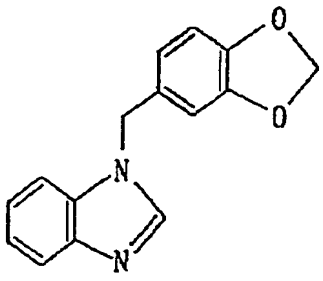
- molecular formula; $C_{16}H_{13}ClN_2O_3$
- yield(%); 26
- m.p.(°C); 133 ~ 134
- Mass m/e; 317 (MH^+)
- NMR δ ($CDCl_3$) ;
  4.21(3H, s), 4.99(2H, s), 5.92(2H, s), 6.65(1H, d, J = 1.6Hz), 6.68(1H, dd, J = 8.0Hz, 1.6Hz), 6.74-(1H, d, J = 8.0Hz), 7.05(1H, d, J = 1.6Hz), 7.10(1H, dd, J = 8.8Hz, 1.6Hz), 7.43(1H, d, J = 8.8Hz)

Example 267 to 280

The following compounds were prepared in a similar manner to those of Examples 263 to 266.

Example 267

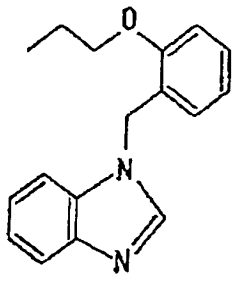
1-(3,4-Methylenedioxybenzyl)benzimidazole



- molecular formula; $C_{15}H_{12}N_2O_2$
- yield(%); 34
- m.p.(°C); 107 ~ 108
- Mass m/e; 253 (MH^+)
- NMR δ ($CDCl_3$) ;
  5.23(2H, s), 5.92(2H, s), 6.63(1H, d, J = 1.6Hz), 6.70(1H, dd, J = 8.0Hz, 1.6Hz), 6.76(1H, d, J = 8.0Hz), 7.23~7.32(3H, m), 7.80~7.83(1H, m), 7.92(1H, s)

Example 268

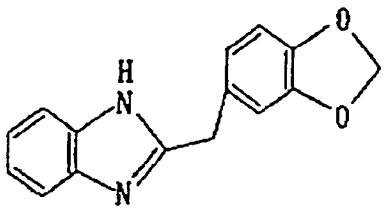
1-(2-Propoxybenzyl)benzimidazole



- molecular formula; $C_{17}H_{18}N_2O$
- yield(%); 89
- m.p.(°C); 85 ~ 86
- Mass m/e; 267 (MH^+)
- NMR δ ($CDCl_3$) ;
  1.02(3H, t, J=7.4Hz), 1.78~1.86(2H, m), 3.95(2H, t, J=6.6Hz), 5.35(2H, s), 6.86~6.90(2H, m), 7.06~7.09(1H, m), 7.23~7.28(3H, m), 7.40~7.43(1H, m), 7.79~7.82(1H, m), 7.99(1H, s)

Example 269

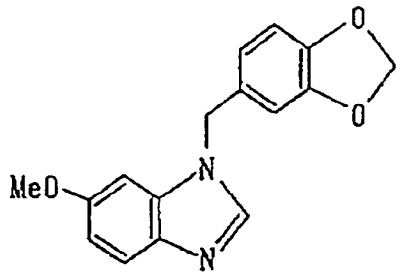
2-(3,4-Methylenedioxybenzyl)benzimidazole



- molecular formula; $C_{15}H_{12}N_2O_2$
- yield(%); 62
- m.p.(°C); 143 ~ 146
- Mass m/e; 253 (MH^+)
- NMR δ (DMSO-d_6) ;
  4.43(2H, s), 5.99(2H, s), 6.89~6.94(2H, m), 7.09(1H, s), 7.48~7.52(2H, m), 7.72~7.76(2H, m)

Example 270

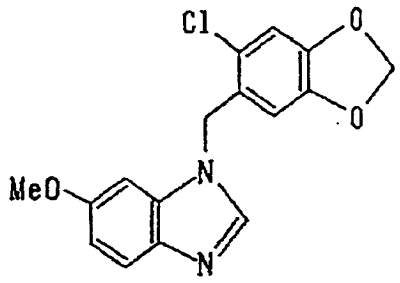
1-(3,4-Methylenedioxybenzyl)-6-methoxybenzimidazole



- molecular formula; $C_{16}H_{14}N_2O_3$
- yield(%); 70
- m.p.(°C); 134 ~ 135
- Mass m/e; 283 $(M+1)^+$
- NMR δ ($CDCl_3$) ;
  3.82(3H, s), 5.21(2H, s), 5.95(2H, s), 6.64(1H, d, J = 1.8Hz), 6.71(1H, dd, J = 7.6Hz, 1.8Hz), 6.75-(1H, d, J = 2.4Hz), 6.78(1H, d, J = 7.6Hz), 6.93(1H, dd, J = 8.8Hz, 2.4Hz), 7.70(1H, d, J = 8.8Hz), 7.90-(1H, s)

Example 271

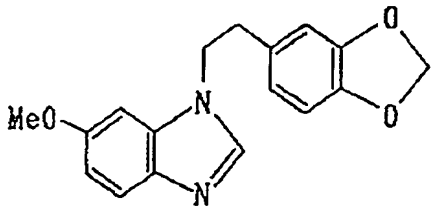
1-(2-Chloro-4,5-methylenedioxybenzyl)-6-methoxybenzimidazole



- molecular formula; $C_{16}H_{13}ClN_2O_3$
- yield(%); 81
- m.p.(°C); 108 ~ 109
- Mass m/e; 317 $(M+1)^+$
- NMR δ ($CDCl_3$) ;
  3.84(3H, s), 5.322(2H, s), 5.97(2H, s), 6.40(1H, s), 6.80(1H, s), 6.91(1H, s), 6.95(1H, d, J = 8.8Hz), 7.72(1H, d, J = 8.8Hz), 7.96(1H, s)

Example 272

1-[2-(3,4-Methylenedioxyphenyl)ethyl]-6-methoxybenzimidazole

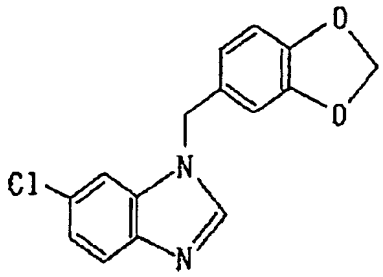


- molecular formula; $C_{17}H_{16}N_2O_3$
- yield(%); 69
- m.p.(°C); oily substance
- Mass m/e; 297 $(M+1)^+$
- NMR δ ($CDCl_3$) ;

3.04(2H, t, J=6.8Hz), 3.87(3H, s), 4.31(2H, t, J=6.8Hz), 5.93(2H, s), 6.43(1H, dd, J=8.0Hz, 2.0Hz), 6.52(1H, d, J=2.0Hz), 6.68(1H, d, J=8.0Hz), 6.77(1H, d, J=2.4Hz), 6.92(1H, dd, J=8.8Hz, 2.4Hz), 7.57(1H, s), 7.67(1H, d, J=8.8Hz)

Example 273

6-Chloro-1-(3,4-methylenedioxybenzyl)benzimidazole

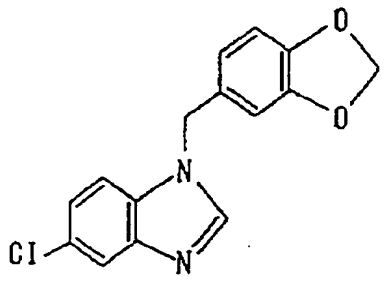


- molecular formula; $C_{15}H_{11}N_2O_2$
- m.p.(°C); 122 ~ 123
- Mass m/e; 287 (MH^+)
- NMR δ ($CDCl_3$) ;

5.18(2H, s), 5.94(2H, s), 6.61(1H, d, J=1.2Hz), 6.68(1H, dd, J=8.0Hz, 1.2Hz), 6.77(1H, d, J=8.0Hz), 7.22~7.40(2H, m), 7.71(1H, d, J=8.8Hz), 7.90(1H, s)

Example 274

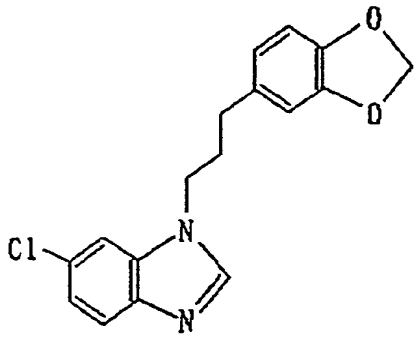
5-Chloro-1-(3,4-methylenedioxybenzyl)benzimidazole



- molecular formula; $C_{15}H_{11}ClN_2O_2$
- yield(%); 83
- m.p.(°C); 113 ~ 114
- Mass m/e; 287 (MH^+)
- NMR δ ($CDCl_3$) ;
  5.20(2H, s), 5.93(2H, s), 6.60(1H, d, J=1.6Hz), 6.67(1H, dd, J=7.6Hz, 1.6Hz), 7.76(1H, d, J=7.6Hz), 7.18~7.20(2H, m), 7.78(1H, s), 7.93(1H, s)

Example 275

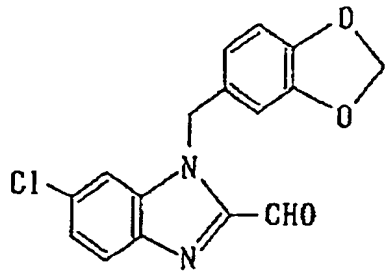
6-Chloro-[3-(3,4-methylenedioxyphenyl)propyl]benzimidazole



- molecular formula; $C_{17}H_{15}ClN_2O_2$
- yield(%); 40
- m.p.(°C); 107 ~ 109
- Mass m/e; 315 (MH^+)
- NMR δ ($CDCl_3$) ;
  2.13~2.21(2H, m), 2.54(2H, t, J=7.4Hz), 4.11(2H, t, J=7.2Hz), 5.94(2H, s), 6.59(1H, dd, J=8.0Hz, 1.6Hz), 6.64(1H, d, J=1.6Hz), 6.75(1H, d, J=8.0Hz), 7.24(1H, dd, J=8.4Hz, 2.0Hz), 7.31(1H, d, J=2.0Hz), 7.71(1H, d, J=8.4Hz), 7.84(1H, s)

Example 276

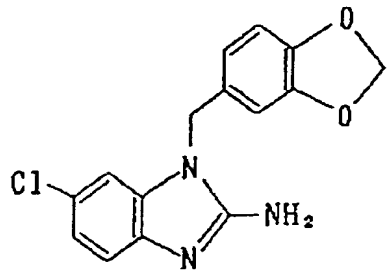
6-Chloro-2-formyl-1-(3,4-methylenedioxybenzyl)benzimidazole



- molecular formula; $C_{16}H_{11}ClN_2O_3$
- yield(%); 55
- m.p.(°C); 120 ~ 122
- Mass m/e; 315 (MH^+)
- NMR δ ($CDCl_3$) ;
  5.71(2H, s), 5.93(2H, s), 6.64(1H, d, J=1.6Hz), 6.70(1H, dd, J=7.6Hz, 1.6Hz), 6.75(1H, d, J=7.6Hz), 7.36(1H, dd, J=8.8Hz, 2.0Hz), 7.46(1H, d, J=2.0Hz), 7.86(1H, d, J=8.8Hz), 10.11(1H, s)

Example 277

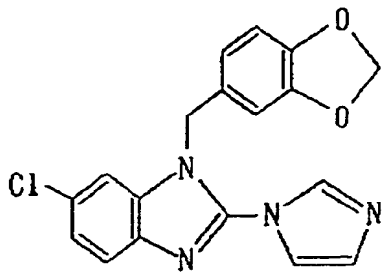
2-Amino-6-chloro-1-(3,4-methylenedioxybenzyl)benzimidazole



- molecular formula; $C_{15}H_{12}ClN_3O_2$
- yield(%); 10
- m.p.(°C); 223 ~ 224
- Mass m/e; 302 (MH^+)
- NMR δ (DMSO-d_6);
  5.13(2H, s), 5.95(2H,s), 6.68~6.71(3H, m), 6.77(1H, d, J=1.6Hz), 6.84(1H, d, J=7.6Hz), 6.90(1H, dd, J=8.4Hz, 2.4Hz), 7.07(1H, d, J=8.4Hz), 7.18(1H, d, J=2.4Hz)

Example 278

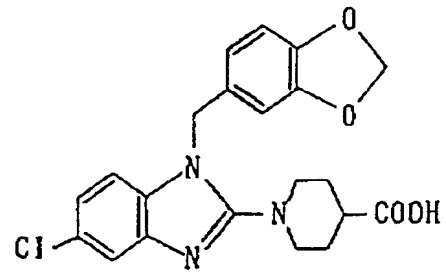
6-Chloro-2-(imidazol-1-yl)-1-(3,4-methylenedioxybenzyl)benzimidazole



- molecular formula; $C_{18}H_{13}ClN_4O_2$
- yield(%); 41
- m.p.(°C); 127 ~ 129
- Mass m/e; 353 (MH^+)
- NMR δ ($CDCl_3$) ;
  5.20(2H, s), 5.97(2H, s), 6.48~6.50(2H, m), 6.76(1H, d, J=7.2Hz), 7.23~7.35(4H, m), 7.72(1H, d, J=8.4Hz), 7.89(1H, s)

Example 279

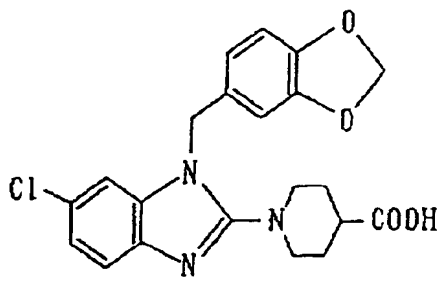
2-(4-Carboxypiperidino)-5-chloro-1-(3,4-methylenedioxybenzyl)benzimidazole



- molecular formula; $C_{21}H_{20}ClN_3O_4$
- yield(%); 84
- m.p.(°C); 201 ~ 202
- Mass m/e; 414 (MH^+)
- NMR δ (DMSO-d_6) ;
  1.64~1.77(2H, m), 1.84-1.90(2H, m), 2.40~2.46(1H, m), 2.92~3.00(2H, m), 3.43~3.47(2H, m), 5.15-(2H, s), 5.96(2H, s), 6.60(1H, dd, J=8.0Hz, 1.6Hz), 6.72(1H, d, J=1.6Hz), 6.82(1H, d, J=8.0Hz), 7.03-(1H, dd, J=8.4Hz, 2.0Hz), 7.18(1H, d, J=8.4Hz), 7.42(1H, d, J=2.0Hz)

Example 280

2-(4-Carboxypiperidino)-6-chloro-1-(3,4-methylenedioxybenzyl)benzimidazole



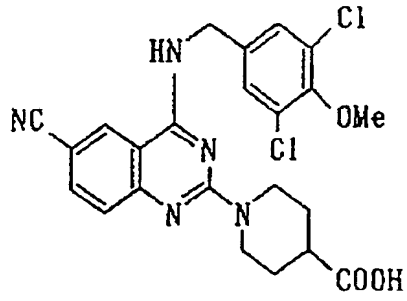
- molecular formula; $C_{21}H_{20}ClN_3O_4$
- m.p.(°C); amorphous
- Mass m/e; 414 (MH^+)
- NMR δ (DMSO-d_6) ;
  1.70~1.79(2H, m), 1.80~1.89(2H, m), 2.31~2.42(1H, m), 2.90~2.97(2H, m), 3.39~3.45(2H, m), 5.15-(2H, s), 5.96(2H, s), 6.61(1H, d, J=8.0Hz), 6.73(1H, s), 6.83(1H, d, J=8.0Hz), 7.06(1H, dd, J=8.4Hz, 2.0Hz), 7.30(1H, d, J=2.0Hz), 7.38(1H, d, J=8.4Hz)

Examples 281 to 291

The following compounds were prepared in a similar manner to those of Examples 88 to 94.

Example 281

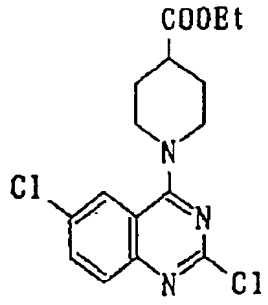
2-(4-Carboxypiperidino)-4-(3,5-dichloro-4-methoxybenzylamino)-6-cyanoquinazoline



- molecular formula; $C_{23}H_{21}Cl_2N_5O_3$
- yield(%); 98
- m.p.(°C); 255 ~ 256 (dec.)
- Mass m/e; 486 $(M+1)^+$
- NMR δ (DMSO-d_6);
  1.36(2H, brm), 1.80(2H, brm), 2.52(1H, m), 3.03(2H, m), 3.78(3H, s), 4.59(2H, d, J=6.0Hz), 4.59-(2H, brm), 7.29(1H, d, J=8.8Hz), 7.50(2H, s), 7.75(1H, dd, J=8.8Hz, 1.6Hz), 8.53(1H, d, J=1.6Hz), 8.85(1H, brt, J=6.0Hz), 12.18(1H, brs)

Example 282

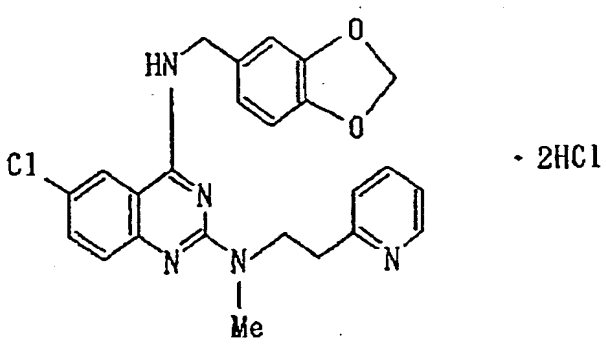
2,6-Dichloro-4-(4-ethoxycarbonylpiperidino)quinazoline



- molecular formula; $C_{16}H_{17}Cl_2N_3O_2$
- yield(%); 100
- m.p.(°C); 101 ~ 103
- Mass m/e; 354 (M+1)
- NMR δ ($CDCl_3$) ;
  1.30(3H, t, J=7.2Hz), 1.99(2H, m), 2.14(2H, m), 2.69(1H, m), 3.35(2H, dt, J=11.2Hz, 2.4Hz), 4.20-(2H, q, J=7.2Hz), 4.31(2H, dt, J=13.6Hz, 3.6Hz), 7.67(1H, dd, J=8.8Hz, 2.2Hz), 7.76(1H, d, J=8.8Hz), 7.79(1H, d, J=2.2Hz)

Example 283

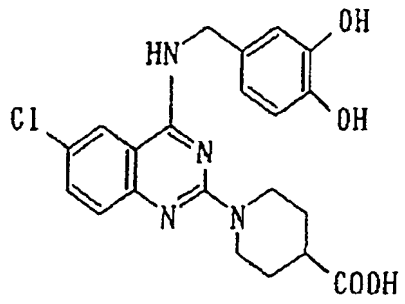
2-[N-[2-(2-Pyridyl)ethyl]methylamino]-4-(3,4-methylenedioxybenzy)]amino-6-chloroquinazoline dihydrochloride



- molecular formula; $C_{24}H_{22}ClN_5O_2 \cdot 2HCl$
- yield(%); 94
- m.p.(°C); 234 ~ 236 (dec.)
- Mass m/e; 448 $(M+1)^+$
- NMR δ (DMSO-d_6) ;
  3.2~3.3(5H, br), 4.12(2H, br), 4.61(2H, br), 5.97(2H, s), 6.82(1H, brd), 6.88(1H, brd), 7.00(1H, s), 7.74(2H, br), 7.86(1H, dd, J=9.2Hz, 2.0Hz), 8.01(1H, br), 8.26(1H, br), 8.57(1H, d, J=2.0Hz), 8.74(1H, br), 10.16(1H, brs), 12.12(1H, brs)

Example 284

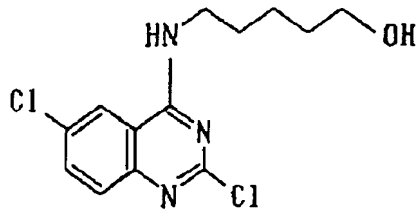
2-(4-Carboxypiperidino)-4-(3,4-dihydroxybenzyl)amino-6-chloroquinazoline



- molecular formula; $C_{21}H_{21}ClN_4O_4$
- yield(%); 95
- m.p.(°C); 216 ~ 218 (dec.)
- Mass m/e; 429 (MH^+)
- NMR δ (DMSO-d_6);
  1.38~1.47(2H, m), 1.80~1.84(2H, m), 2.44~2.49(1H, m), 2.93~3.00(2H, m), 4.48(2H, d, J=5.6Hz), 4.57~4.61(2H, m), 6.60~6.65(2H, m), 6.74(1H, d, J=1.6Hz), 7.24(1H, d, J=8.8Hz), 7.46(1H, dd, J=8.8Hz, 2.0Hz), 8.15(1H, d, J=2.0Hz), 8.48(1H, brs), 8.675(1H, s), 8.75(1H, s), 12.14(1H, brs)

Example 285

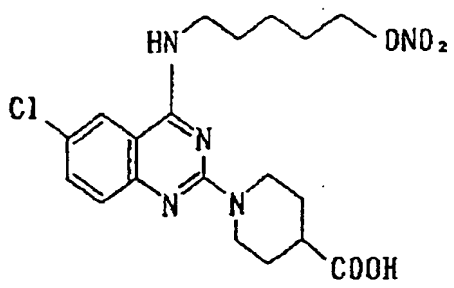
2,6-Dichloro-4-(5-hydroxypentyl)aminoquinazoline



- molecular formula; $C_{13}H_{15}Cl_2N_3O$
- yield(%); 82
- m.p.(°C); 134 ~ 135
- Mass m/e; 300 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.53(2H, m), 1.65(2H, m), 1.76(2H, m), 3.63(2H, m), 3.66(2H, m), 7.61(1H, dd, J=8.8Hz, 2.4Hz), 7.67(1H, d, J=8.8Hz), 7.85(1H, brs), 8.20(1H, d, J=2.4Hz)

Example 286

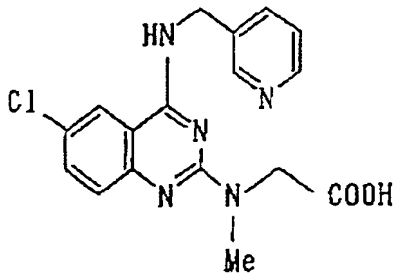
2-(4-Carboxypiperidino)-4-(5-nitroxypentyl)amino-6-chloroquinazoline



- molecular formula; $C_{19}H_{24}ClN_5O_5$
- yield(%); 80
- m.p.(°C); 176 ~ 179 (dec.)
- Mass m/e; 438 (MH^+)
- NMR δ (DMSO-d_6) ;
  1.34~2.00(10H, m), 2.57~2.64(1H, m), 3.18~3.59(4H, m), 4.44~4.58(4H, m), 7.72~7.86(2H, m), 8.39~8.41(1H, m), 12.31(2H, brs)

Example 287

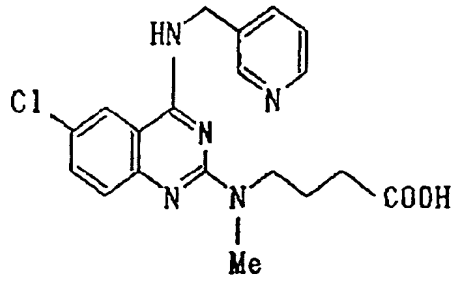
2-(Carboxymethyl)methylamino-4-(3-pyridylmethyl)amino-6-chloroquinazoline



- molecular formula; $C_{17}H_{16}ClN_5O_2$
- yield(%); 97
- m.p.(°C); 222 ~ 223
- Mass m/e; 358 (M + 1)
- NMR δ (DMSO-d_6) ;
  3.10(3H, s), 4.22(2H, brs), 4.63(2H, brs), 7.31(2H, m), 7.48(1H, m), 7.72(1H, m), 8.14(1H, d, J = 2.4Hz), 8.43(1H, d, J = 4.8Hz), 8.59(1H, m), 8.66(1H, brs)

Example 288

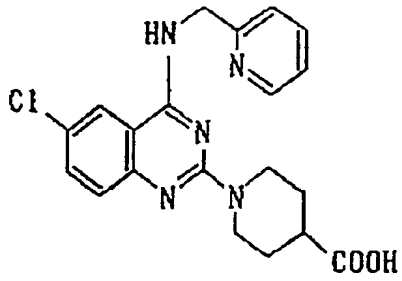
2-[N-(3-Carboxypropyl)-N-methylamino]-4-(3-pyridylmethyl)amino-6-chloroquinazoline



- molecular formula; $C_{19}H_{20}ClN_5O_2$
- yield(%); 41
- m.p.(°C); 110 ~ 112
- Mass m/e; 386 (M+1)
- NMR δ (DMSO-d_6) ;
  1.67(2H, brs), 2.09(2H, m), 3.02(3H, s), 3.53(2H, t, J=6.8Hz), 4.67(2H, d, J=5.6Hz), 7.24(2H, d, J=8.8Hz), 7.31(1H, dd, J=8.0Hz, 4.8Hz), 7.47(1H, dd, J=8.8Hz, 2.0Hz), 7.73(1H, d, J=8.0Hz), 8.13-(1H, d, J=2.0Hz), 8.41(1H, d, J=4.8Hz), 8.58(1H, s), 8.62(1H, brs), 12.04(1H, brs)

Example 289

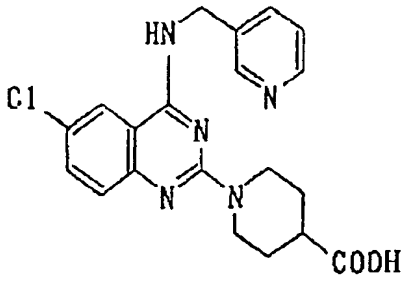
2-(4-Carboxypiperidino)-4-(2-pyridylmethyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{20}ClN_5O_2$
- yield(%); 92
- m.p.(°C); 235 ~ 237
- Mass m/e; 398 (M+1)
- NMR δ (DMSO-d_6) ;
  1.25~1.45(2H, m), 1.71~1.83(2H, m), 2.45~2.54(1H, m), 2.93~3.10(2H, m), 4.37~4.48(2H, m), 4.77-(2H, d, J=5.5Hz), 7.25(1H, dd, J=7.7Hz, 5.0Hz), 7.37(1H, d, J=7.7Hz), 7.48(1H, brs), 7.63(1H, brs), 7.73(1H, td, J=7.7Hz, 1.6Hz), 8.34(1H, brs), 8.51(1H, brd, J=5.0Hz), 12.23(1H, brs)

Example 290

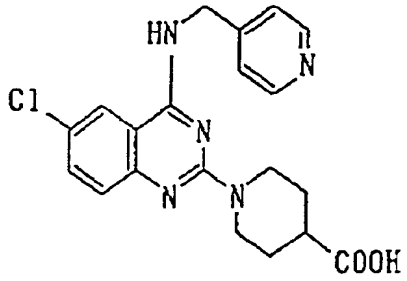
2-(4-Carboxypiperidino)-4-(3-pyridylmethyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{20}ClN_5O_2$
- yield(%); 93
- m.p.(°C); >250
- Mass m/e; 398 (M + 1)
- NMR δ (DMSO-d_6);
  1.45~1.60(2H, m), 1.84~1.97(2H, m), 2.58~2.68(1H, m), 3.25~3.45(2H, m), 4.45~4.54(2H, m), 4.80-(2H, d, J = 5.7Hz), 7.41(1H, dd. J = 7.9Hz, 4.8Hz), 7.82(1H, dd, J = 9.0Hz, 2.0Hz), 7.86~7.96(2H, m), 8.50(1H, d, J = 4.8Hz), 8.55(1H, d, J = 1.6Hz), 8.69(1H, s)

Example 291

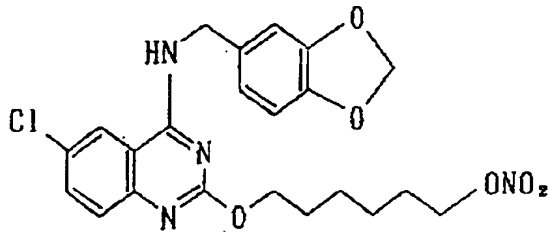
2-(4-Carboxypiperidino)-4-(4-pyridylmethyl)amino-6-chloroquinazoline



- molecular formula; $C_{20}H_{20}ClN_5O_2$
- yield(%); 89
- m.p.(°C); 167 ~ 168
- Mass m/e; 398 (M + 1)
- NMR δ (DMSO-d_6) ;
  1.24~1.36(2H, m), 1.68~1.77(2H, m), 2.40~2.49(1H, m), 2.86-2.96(2H, m), 4.42~4.50(2H, m), 4.66-(2H, d, J = 5.7Hz), 7.28(1H, d, J = 9.0Hz), 7.34(2H, d, J = 6.0Hz), 7.51(1H, dd, J = 9.0Hz, 2.4Hz), 8.18-(1H, d, J = 2.4Hz), 8.47(2H, d, J = 6.0Hz), 8.74(1H, t, J = 5.7Hz)

Example 292

2-(6-Nitroxyhexyloxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



860 mg of 2-(6-hydroxyhexyloxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline was dissolved in 15 ml of pyridine, followed by the addition of 570 mg of methyl chloride under cooling with ice. The obtained mixture was stirred for 10 hours, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated to give 1.2 g of crude 2-(6-tosyloxyhexyloxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline.

3 g of sodium iodide and 30 ml of dimethylformamide were added to the crude product. The obtained mixture was maintained at 60 °C by heating for one hour, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous solution of sodium chloride, dried and concentrated. The residue was purified by silica gel column chromatography to give 450 mg of 2-(6-iodohexyloxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline.

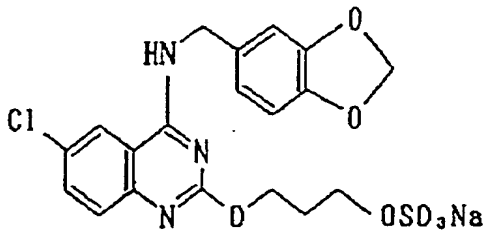
410 mg of the 2-(6-iodohexyloxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline was suspended in 15 ml of acetonitrile, followed by the addition of 900 mg of silver nitrate. The obtained mixture was maintained at 60 °C by heating for one hour, followed by the addition of water and ethyl acetate. The resulting mixture was filtered through Celite to remove insolubles. The organic layer was recovered, dried and subjected to silica gel column chromatography to give 340 mg of the title compound.

- molecular formula; $C_{22}H_{23}ClN_4O_6$ (474.5)
- yield(%); 95
- m.p.(°C); 121 ~ 122
- Mass; 475 (MH^+)
- NMR δ ($CDCl_3$);

  1.42 ~ 1.59 (4H, m), 1.70 ~ 1.89 (4H, m), 4.43 (4H, q, J=6.8Hz), 4.73 (2H, d, J=4.4Hz), 5.95 (2H, s), 6.28 (1H, br), 6.77 (1H, d, J=8.0Hz), 6.83 (1H, d, J=8.0Hz), 6.85 (1H, s), 7.54 (1H, d, J=8.8Hz), 7.58 (1H, d, J=8.8Hz), 7.66 (1H, s)

Example 293

Sodium 2-(3-sulfoxypropoxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



1 g of 2-(3-hydroxypropoxy)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline and 540 mg of sulfur trioxide/trimethylamine complex were suspended in 10 ml of pyridine. The obtained suspension was stirred at room temperature overnight, followed by the addition of ethyl acetate. The crystals thus precipitated were recovered by filtration, suspended in methanol and dissolved therein by the addition of 1N

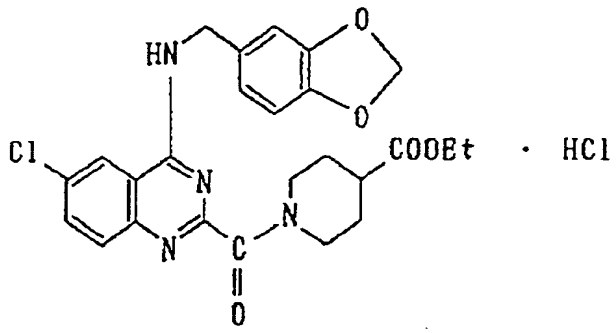
sodium hydroxide. Ether was added to the obtained solution to precipitate crystals. The crystals were recovered by filtration, whereby 400 mg (32%) of the title compound was obtained.

- molecular formula; $C_{19}H_{17}ClN_3NaO_7S$ (489.5)
- yield(%); 32
- m.p.(°C); 190 ~ 192 (dec.)
- Mass; 490 (MH^+)
- NMR δ (DMSO-d_6);

  1.90 ~ 1.95 (2H, m), 3.82 (2H, t, J=6.4Hz), 4.28 (2H, t, J=6.8Hz), 4.61 (2H, d, J=5.6Hz), 5.95 (2H, s), 6.84 (2H, s), 6.98 (1H, s), 7.50 (1H, d, J=8.8Hz), 7.64 (1H, dd, J=8.8Hz, 2.4Hz), 8.84 (1H, d, J=2.4Hz), 8.79 (1H, t J=1.6Hz)

Example 294

2-(4-Ethoxycarboxypiperidino)carbonyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride



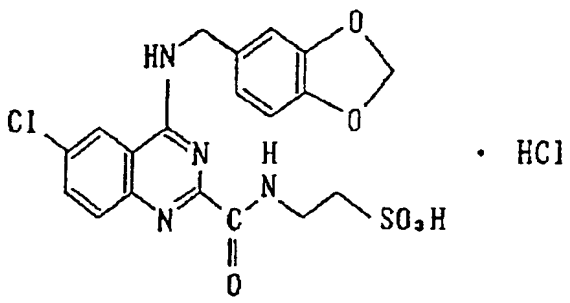
A solution of 0.50 ml (3.3 mmol) of diethyl cyanophosphate in 3 ml of dimethylformamide and 0.50 ml (3.6 mmol) of triethylamine were dropped, in this order, into a solution of 0.78 g (2.2 mmol) of 2-carboxy-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline and 0.50 g (3.2 mmol) of ethyl isonipecotate in 7 μl of dimethylformamide under cooling with ice and stirring. The obtained mixture was stirred under cooling with ice for 30 minutes and thereafter at room temperature for 3 hours, followed by the addition of water. The resulting mixture was extracted with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled in a vacuum to remove the solvent. The residue was recrystallized from hydrochloric acid/ethanol/ether to give 0.96 g of the title compound.

- molecular formula; $C_{25}H_{25}ClN_4O_5 \cdot HCl$
- yield(%); 82
- m.p.(°C); 205 ~ 206 (dec.)
- Mass m/e; 497 $(M+1)^+$
- NMR δ (DMSO-d_6) ;

  1.18(3H, t, J=7.2Hz), 1.51(2H, m), 1.70(1H, m), 1.95(1H, m), 2.66(1H, m), 3.02(1H, m), 3.11(1H, m), 3.62(1H, m), 4.08(2H, q, J=7.2Hz), 4.31(1H, m), 4.71(1H, dd, J=14.9Hz, 6.0Hz), 4.78(1H, dd, J=14.9Hz, 6.0Hz), 5.97(2H, s), 6.84(1H, d, J=8.0Hz), 6.87(1H, dd, J=8.0Hz, 1.2Hz), 6.97(1H, d, J=1.2Hz), 7.82(1H, d, J=9.2Hz), 7.97(1H, dd, J=9.2Hz, 2.0Hz), 8.67(1H, d, J=2.0Hz), 10.13(1H, brs)

Example 295

2-[N-(2-Sulfoethyl)carbamoyl]-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride



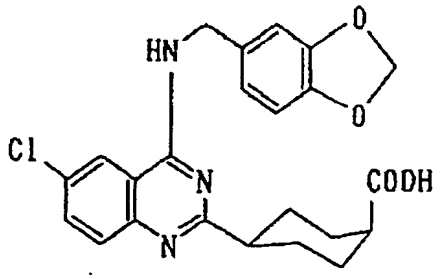
0.60 ml (3.8 mmol) of diethyl cyanophosphate and 0.90 ml (6.4 mmol) of triethylamine were dropped, in this order, into a solution of 0.50 g (1.4 mmol) of 2-carboxy-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline and 0.28 g (1.9 mmol) of sodium 2-aminoethanesulfonate in 15 ml of dimethylformamide under cooling with ice and stirring. The obtained mixture was stirred at room temperature for several days, followed by the addition of 10 ml of 1N hydrochloric acid and water. The crystals thus precipitated were recovered by filtration, washed with water and air-dried to give 0.61 g of the title compound.

- molecular formula; $C_{19}H_{17}ClN_4O_5S \cdot HCl$
- yield(%); 93
- NMR δ (DMSO-d_6) ;

  2.76(2H, t, J=6.4Hz), 3.67(2H, q, J=6.4Hz), 5.01(2H, d, J=5.6Hz), 5.99(2H, s), 6.88(1H, d, J=7.6Hz), 7.05(1H, dd, J=7.6Hz, 1.6Hz), 7.11(1H, d, J=1.6Hz), 8.09(1H, dd, J=8.8Hz, 2.0Hz), 8.13-(1H, d, J=8.8Hz), 8.68(1H, d, J=2.0Hz), 9.97(1H, t, J=5.6Hz), 10.55(1H, brs)

Example 296

2-(4-cis-Carboxycyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



a) 2-(4-Ethoxycarbonylcyclohexylcarbonyl)amino-5-chlorobenzamide

1.5 g of 4-ethoxycarbonylcyclohexanecarbonyl chloride was added to a mixture comprising 1.23 g of 2-amino-5-chlorobenzamide hydrochloride, 3 ml of N,N-diisopropylethylamine and 100 ml of tetrahydrofuran at room temperature. The obtained mixture was reacted at room temperature overnight, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and concentrated. The residue was subjected to silica gel chromatography with 30 to 35% ethyl acetate/hexane to give 1.5 g of the title compound (as a cis/trans mixture).

b) 2-(4-Ethoxycarbonylcyclohexyl)-6-chloroquinazolin-4-one

1.3 g of the compound prepared in the step (a) was suspended in 20 ml of ethanol. 320 mg of potassium t-butoxide was added to the obtained suspension in three portions at room temperature. The resulting mixture was reacted at room temperature overnight. The reaction mixture was partially concentrated, followed by the addition of water and 3.5 ml of 1N hydrochloric acid in this order. The crystals thus precipitated were recovered by filtration, washed with water, and vacuum-dried over phosphorus pentaoxide to give 1.16 g of the title compound (as a cis/trans mixture).

c) 2-(4-cis-Ethoxycarbonylcyclohexyl)-4,6-dichloroquinazoline

20 ml of phosphorus oxychloride was added to 1.0 g of the compound prepared in the step (b). The obtained mixture was heated under reflux for 2 hours and concentrated. 50 ml of chloroform was added to the residue to form a solution, which was poured into a saturated aqueous solution of sodium hydrogencarbonate cooled with ice. The chloroform layer was recovered and the aqueous layer was extracted with 30 ml of chloroform. The chloroform layers were combined, washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and filtered through a silica gel bed. The silica gel was washed with 10% ethyl acetate/hexane. The washings and the filtrate were combined and concentrated. The residue was subjected to silica gel column chromatography with 5% ethyl acetate/hexane to give 145 mg of the title compound.

- NMR δ ($CDCl_3$) ;
  1.28(3H, t, J=7.2Hz), 1.69~1.78(2H, m), 1.92~2.02(2H, m), 2.05~2.21(4H, m), 2.61~2.68(1H, m), 3.05~3.13(1H, m), 4.17(2H, q, J=7.2Hz), 7.83(1H, dd, J=9.2Hz, 2.4Hz), 7.94(1H, d, J=9.2Hz), 8.19-(1H, d, J=2.4Hz)

Simultaneously, 470 mg of 2-(4-trans-ethoxycarbonylcyclohexyl)-4,6-dichloroquinazoline was obtained as a more highly polar component.

- NMR δ ($CDCl_3$) ;
  1.28(3H, t, J=7.2Hz), 1.57~1.69(2H, m), 1.71~1.84(2H, m), 2.13~2.24(4H, m), 1.41(1H, tt, J=12.2Hz, 3.5Hz), 2.99(1H, tt, J=12.2Hz, 3.5Hz), 4.15(2H, q, J=7.2Hz), 7.84(1H, dd, J=9.2Hz, 2.4Hz), 7.94(1H, d, J=9.2Hz), 8.20(1H, d, J=2.4Hz)

d) 2-(4-cis-Ethoxycarbonylcyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

A mixture comprising 145 mg of the compound prepared in the step (c), 80 mg of 3,4-methylenedioxybenzylamine, 20 μl of triethylamine and 5 ml of isopropyl alcohol was maintained at 80°C for 3 hours to conduct a reaction. The reaction mixture was concentrated and extracted with ethyl acetate/water. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was subjected to silica gel column chromatography with 15% ethyl acetate/hexane to give 190 mg of the title compound.

- NMR δ ($CDCl_3$) ;
  1.25(3H, t, J=7.2Hz), 1.66~1.75(2H, m), 1.84~1.72(2H, m), 2.05~2.23(4H, m), 2.60~2.66(1H, m), 2.85~2.93(1H, m), 4.15(2H, q, J=7.2Hz), 4.74(2H, d, J=5.6Hz), 5.72(1H, t, J=5.6Hz), 5.96(2H, s), 6.79(1H, d, J=8.0Hz), 6.85~6.90(2H, m), 7.58~7.62(2H, m), 7.74(1H, d, J=9.6Hz)

e) 2-(4-cis-Carboxycyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

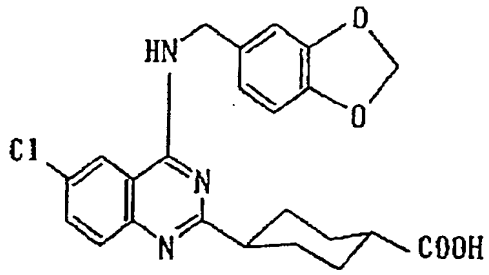
25 ml of ethanol and 2 ml of a 1N aqueous solution of sodium hydroxide were added to the compound prepared in the step (d). The obtained mixture was maintained at 60°C for 8 hours and thereafter heated under reflux for 3 hours to conduct a reaction. The reaction mixture was cooled to room temperature, followed by the addition of 2 ml of 1N aqueous hydrochloric acid. The resulting mixture was partially concentrated to precipitate crystals. The crystals were recovered by filtration, washed with water and diethyl ether, and vacuum-dried over phosphorus pentaoxide to give 138 mg of the title compound.

- molecular formula; $C_{23}H_{22}ClN_3O_4$
- yield(%); 77
- m.p.(°C); 152 ~ 153
- Mass m/e; 440 (M+1)
- NMR δ (DMSO-d_6) ;
  1.54~1.64(2H, m), 1.66~1.76(2H, m), 1.89~2.02(4H, m), 2.69~2.77(1H, m), 4.63(2H, d, J=5.6Hz),

5.96(2H, s), 6.84(1H, d, J=8.0Hz) 6.89(1H, dd, J=8.0Hz, 1.6Hz), 6.95(1H, d, J=1.6Hz), 7.63(1H, d, J=8.8Hz), 7.71(1H, dd, J=8.8Hz, 2.4Hz), 8.36(1H, d, J=2.4Hz), 8.71(1H, t, J=5.6Hz)

Example 297

2-(4-trans-Carboxycyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



a) 2-(4-trans-Ethoxycarbonylcyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

145 mg of the trans isomer prepared in the step (c) of Example 296 was treated in a similar manner to that of the step (d) of Example 296 to give 180 mg of the title compound.

- NMR δ ($CDCl_3$) ;

  1.27(3H, t, J=7.2Hz), 1.54~1.67(2H, m), 1.70~1.83(2H, m), 2.08~2.17(4H, m), 2.39(1H, tt, J=12.2Hz, 3.2Hz), 2.79(1H, tt, J=12.2Hz, 3.2Hz), 4.14(2H, q, J=7.2Hz), 4.76(2H, d, J=5.5Hz), 5.82-(1H, t, J=5.5Hz), 5.96(2H, s), 6.79(1H, d, J=7.9Hz), 6.86(1H, dd, J=7.9Hz, 1.6Hz), 6.90(1H, d, J=1.6Hz), 7.59~7.63(2H, m), 7.73(1H, d, J=7.9Hz)

b) 2-(4-Trans-carboxycyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

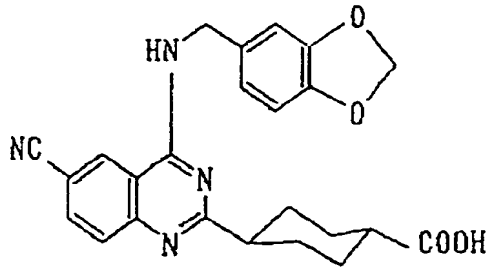
The compound prepared in the step (a) was hydrolyzed in a similar manner to that of the step (e) of Example 296 to give 163 mg of the title compound.

- molecular formula; $C_{23}H_{22}ClN_3O_4$
- yield(%); 96
- m.p.(°C); 245 ~ 246
- Mass m/e; 440 (M+1)
- NMR δ (DMSO-d_6) ;

  1.38~1.50(2H, m), 1.55~1.68(2H, m), 1.94~2.04(4H, m), 2.34(1H, tt, J=11.9Hz, 3.1Hz), 2.60(1H, tt, J=11.9Hz, 3.1Hz), 4.66(2H, d, J=5.7Hz), 5.97(2H, s), 6.85(1H, d, J=8.1Hz), 6.88(1H, dd, J=8.1Hz, 1.5Hz), 6.98(1H, d, J=1.5Hz), 7.63(1H, d, J=9.0Hz), 7.72(1H, dd, J=9.0Hz, 2.4Hz), 8.37(1H, d, J=2.4Hz), 8.71(1H, brt, J=5.7Hz), 12.04(1H, s)

Example 298

2-(4-trans-Carboxycyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline



a) 4-(4-methoxycarbonylcyclohexanecarbonyl)amoinobenzene-1,3-dicarboxamide

5.1 g of 4-methoxycarbonylcyclohexanecarbonyl chloride was added to a mixture comprising 3.6 g of 4-aminobenzene-1,3-dicarboxamide, 5 ml of N,N-dimethylaniline and 50 ml of tetrahydrofuran at room temperature. The obtained mixture was reacted as such overnight, followed by the addition of water. The crystals thus precipitated were recovered by filtration, washed with water and diethyl ether, and dried to give 5.77 g of the title compound.

b) 2-(4-Methyoxycarbonylcyclohexyl)-6-carbamoylquinazolin-4-one

5.7 g of the compound prepared in the step (a) was suspended in 200 ml of methanol, followed by the addition of 1.84 g of potassium t-butoxide. The obtained mixture was reacted at room temperature overnight, followed by the addition of water. The resulting mixture was acidified with concentrated hydrochloric acid to precipitate crystals. The crystals were recovered by filtration, washed with water and diethyl ether, and dried to give 5.04 g of the title compound.

c) 2-(4-trans-Methoxycarbonylcyclohexyl)-4-chloro-6-cyanoquinazoline

A mixture comprising 2.0 g of the compound prepared in the step (b), 2.0 g of lithium chloride and 40 ml of phosphorus oxychloride was heated under reflux for 6 hours and filtered to remove insolubles. The filtrate was concentrated and the residue was subjected to silica gel column chromatography with 10% ethyl acetate/hexane, whereby the trans isomer was separated from the cis isomer. 180 mg of the title compound was obtained.

- NMR δ ($CDCl_3$) ;
  1.57~1.70(2H, m), 1.72~1.84(2H, m), 2.12~2.26(4H, m), 2.43(1H, tt, J = 12.3Hz, 3.2Hz), 3.03(1H, tt, J = 11.9Hz, 3.0Hz), 3.71(3H, s), 8.04(1H, dd, J = 8.8Hz, 1.6Hz), 8.08(1H, dd, J = 8.8Hz, 0.5Hz), 8.62(1H, dd, J = 1.6Hz, 0.5Hz)

d) 2-(4-trans-Methoxycarbonylcyclohexyl)-4-(3,4-methylenedioxybenzyl)amino-6-cyanoquinazoline

A mixture comprising 180 mg of the compound prepared in the step (c), 100 mg of 3,4-methylenedioxybenzylamine, 200 μl of triethylamine and 5 ml of isopropyl alcohol was maintained at 80 °C for one hour to conduct a reaction. The reaction mixture was concentrated and extracted with ethyl acetate/water. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was subjected to silica gel column chromatography with 10% ethyl acetate/benzene to give 157 mg of the title compound.

- NMR δ ($CDCl_3$) ;
  1.55~1.68(2H, m), 1.70~1.82(2H, m), 2.10~2.18(4H, m), 2.42(1H, tt, J = 12.3Hz, 3.2Hz), 2.81(1H, tt, J = 11.9Hz, 3.0Hz), 3.70(3H, s), 4.78(2H, d, J = 5.5Hz), 6.96(2H, s), 6.20(1H, t, J = 5.5Hz), 6.80(1H, d, J = 7.9Hz), 6.88(1H, dd, J = 7.9Hz, 1.6Hz), 6.90(1H, d, J = 1.6Hz), 7.82(2H, s), 8.11(1H, s)

e) 2-(4-trans-Carboxycyclohexyl)-4-(3,4-methylenedioxy benzyl)amino-6-cyanoquinazoline

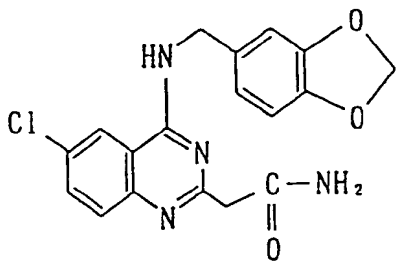
A mixture comprising 157 mg of the compound prepared in the step (d), 1 ml of a 1N aqueous solution of sodium hydroxide, 3 ml of methanol and 6 ml of tetrahydrofuran was reacted at room temperature for 24 hours. 1 ml of 1N hydrochloric acid and 5 ml of water were added to the reaction mixture in this order to precipitate crystals. The crystals were recovered by filtration, washed with water, and dried to give 138 mg of the title compound.

- molecular formula; $C_{24}H_{22}N_4O_4$
- yield(%); 91
- m.p.(°C); 269 ~ 270
- Mass m/e; 431 (M+1)
- NMR δ (DMSO-d_6) ;

1.38~1.50(2H, m), 1.55~1.68(2H, m), 1.95~2.04(4H, m), 2.24(1H, tt, J=11.9Hz, 3.1Hz), 2.63(1H, tt, J=11.9Hz, 3.1Hz), 4.68(2H, d, J=5.7Hz), 5.97(2H, s), 6.86(1H, d, J=7.9Hz), 6.90(1H, dd, J=7.9Hz, 1.5Hz), 6.99(1H, d, J=1.5Hz), 7.71(1H, d, J=8.8Hz), 8.01(1H, dd, J=8.8Hz, 1.6Hz), 8.82(1H, d, J=1.6Hz), 8.95(1H, t, J=5.7Hz)

Example 299

2-Carbamoylmethyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline



a) 2-Ethoxycarbonylmethyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

The title compound was prepared in a similar manner to that of Example 296.

- NMR δ ($CDCl_3$) ;

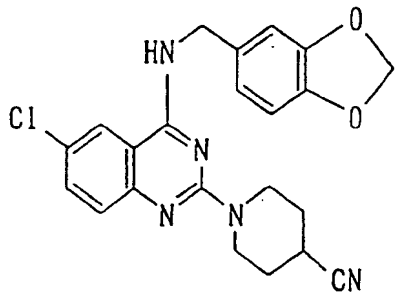
1.27(3H, t, J=7.1Hz), 3.93(2H, s), 4.22(2H, q, J=7.1Hz), 4.71(2H, d, J=5.5Hz), 5.83(1H, t, J=5.5Hz), 5.96(2H, s), 6.78(1H, d, J=7.9Hz), 6.85(1H, dd, J=7.9Hz, 1.6Hz), 6.89(1H, d, J=1.6Hz), 7.60~7.65(2H, m), 7.74(1H, d, J=9.0Hz)

b) 2-Carbamoylmethyl-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

A mixture comprising 200 mg of the compound prepared in the step (a) and 20 ml of ethanol was cooled with ice. Ammonium gas was introduced into the resulting mixture to saturate the mixture therewith. The resulting mixture was gradually brought to room temperature and reacted for 3 days. The reaction mixture was concentrated and the residue was subjected to silica gel column chromatography with 0 to 20% ethanol/ethyl acetate to give 24 mg of the title compound.

Example 300

2-(4-Cyanopiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline

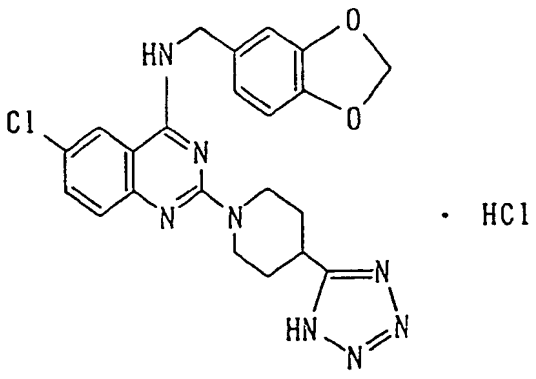


75 ml of thionyl chloride and 150 ml of acetonitrile were added to 3.8 g (0.0086 mol) of 2-(4-carbamoylpiperidino)-4-(3,4-methylenedioxybenzyl) amino-6-chloroquinazoline. The mixture thus obtained was heated under reflux for one hour. The reaction mixture was distilled under a reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogencarbonate and triethylamine were added to the residue and the resultant mixture was etracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure to remove the solvent. The obtained residue was purified by a silica gel column chromatography (ethyl acetate-n-hexane) and recrystallized from chloroform-n-hexane to give 3.1 g of the title compound.

- molecular formula; $C_{22}H_{20}ClN_5O_2$
- yield(%); 85
- m.p.(°C); 169 ~ 170
- NMR δ ($CDCl_3$);
  1.88 (2H,m), 1.95 (2H, m), 2.87 (1H, m), 3.73 (2H, m), 4.25 (2H, m), 4.67 (2H, d, J=5.6Hz), 5.65 (1H, t, J=5.6Hz), 5.97 (2H, s), 6.79 (1H, d, J=8.0Hz), 6.84 ((1H, dd, J=8.0Hz, 1.6Hz), 6.87 (1H, d, J=1.6Hz), 7.39 (1H, d, J=8.8Hz), 7.44 (1H, d, J=2.4Hz), 7.46 (1H, dd, J=8.8Hz, 2.4Hz)

Example 301

2-[4-(1H-tetrazol-5-yl)piperidinol-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride



10 ml of toluene was added to a mixture comprising 0.50 g (0.0012 mol) of 2-(4-cyanopiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline and 0.50 g (0.0024 mol) of trimethyl stannylazide. The mixture thus obtained was heated under reflux for two days. The reaction mixture was distilled under a

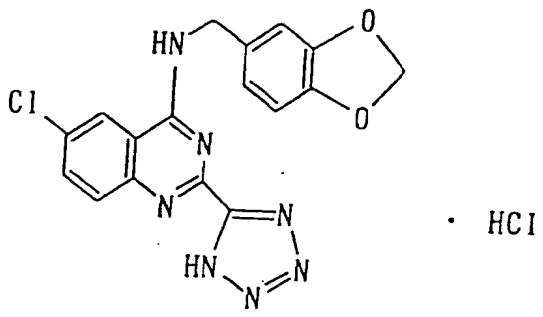
reduced pressure to remove the solvent. The residue was suspended in 10 ml of ethanol, followed by the addition of 10 ml of 1N hydrochloric acid. The mixture thus obtained was stirred at room temperature for several hours. The mixture was filtered to recover the crystal. The crystal was washed with water and air-dried to give 0.60 g of the title compound.

- molecular formula; $C_{22}H_{21}ClN_8O_2 \cdot HCl$
- yield(%); quantitative
- m.p.(°C); 212 ~ 214
- Mass m/e; 465 $(M+1)^+$
- NMR δ (DMSO-d_6);

1.80 (2H,m), 2.17 (2H, m), 3.45 (2H, m), 4.62 (2H, m), 4.69 (2H, d, J=5.6Hz), 5.97 (2H, s), 6.86 (1H, d, J=7.6Hz), 6.91 ((1H, dd, J=7.6Hz, 1.6Hz), 7.01 (1H, d, J=1.6Hz), 7.84 (1H, dd, J=8.8Hz, 1.6Hz), 7.88 (1H, d, J=8.8Hz), 8.51 (1H, d, J=1.6Hz), 10.13 (1H, brs), 12.28 (1H, brs)

Example 302

2-(1H-tetrazol-5-yl)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline hydrochloride



· HCl

The title compound was prepared in a similar manner to that of Example 301.

- molecular formula; $C_{17}H_{12}ClN_7O_2 \cdot HCl$
- yield(%); 37
- m.p.(°C); 201 ~ 204 (dec.)
- Mass m/e; 382 $(MH)^+$
- NMR δ (DMSO-d_6);

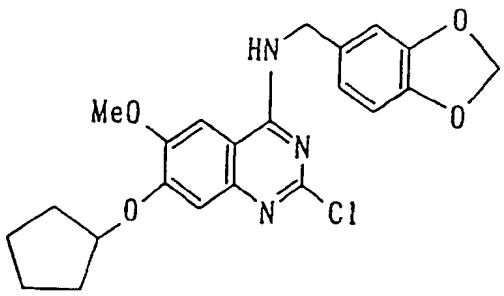
4.90 (2H, d, J=5.6Hz), 5.97 (2H, s), 6.87 (1H, d, J=8.0Hz), 6.98 ((1H, dd, J=8.0Hz, 2.0Hz), 7.11 (1H, d, J=2.0Hz), 7.92 ~ 7.94 (2H, m), 8.60 (1H, d, J=1.6Hz), 9.53 (1H, brs)

Examples 303 to 410

The following compounds were each prepared by any method described above.

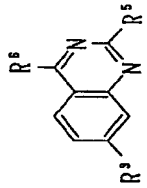
Example 303

2-Chloro-4-(3,4-methylenedioxybenzyl)amino-6-methoxy-7-cyclopentyloxyquinazoline



- molecular formula; $C_{22}H_{22}ClN_3O_4$
- yield(%); 88
- m.p.(°C); 176 ~ 177
- Mass; 428 $(M+1)^+$
- NMR δ ($CDCl_3$);
  1.64 (2H, m), 1.82 (2H, m), 1.93 (2H, m), 2.02 (2H, m), 3.90 (3H, s), 4.74 (2H, d, J=5.6Hz), 4.85 (1H, m), 5.72 (1H, t, J=5.6Hz), 5.96 (2H, s), 6.79 (1H, d, J=7.6Hz), 6.79 ((1H, s), 6.87 (1H, dd, J=7.6Hz, 1.6Hz), 6.90 (1H, d, J=1.6Hz), 7.11 (1H, s)

Table 7



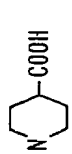
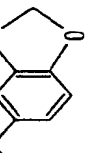
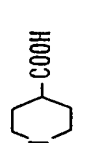
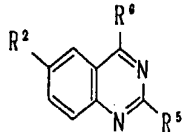
Ex.	R^3	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
304	Cl			264-265	97	441(M+1)	δ(DMSO-d_6) : 1.70(2H,brs), 1.90(2H,m), 2.54(1H,m) 3.11(2H,m), 3.98(2H,m) 4.40(2H,d,J=6.4Hz), 5.93(2H,s) 6.80(2H,brs), 6.84(1H,brs) 7.02(1H,m), 7.28(1H,m), 7.44(1H,brs) 7.68(1H,d,J=8.8Hz), 12.24(1H,brs)	
305	Cl			258-259	97	441(M+1)	δ(DMSO-d_6) : 1.36(2H,m), 1.79(2H,m), 2.47(1H,m) 2.96(2H,t,J=11.2Hz) 4.55(2H,d,J=5.6Hz), 4.58(2H,m) 5.93(2H,s), 6.82(2H,s) 6.92(1H,s) 7.05(1H,dd,J=8.8Hz,2.4Hz) 7.23(1H,d,J=2.4Hz) 8.00(1H,d,J=8.8Hz) 8.58(1H,t,J=5.6Hz), 12.15(1H,brs)	

Table 8



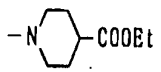
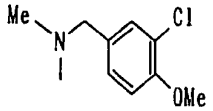
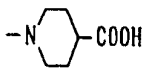
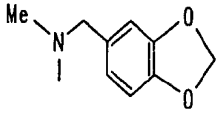
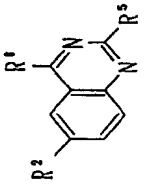
Ex.	R^2	R^5	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
306	CN			amorphous	93	494(MH⁺)	δ(CDCl₃) : 1.25(3H, t, J=7.2Hz), 1.64-1.77(2H, m) 1.94-2.01(2H, m), 2.52-2.61(1H, m) 3.04-3.14(2H, m), 3.25(3H, s) 3.91(3H, s), 4.14(3H, q, J=7.2Hz) 4.72-4.81(2H, m), 4.74(2H, s) 6.93(1H, d, J=8.4Hz) 7.19(1H, dd, J=8.4Hz, 2.0Hz) 7.37(1H, d, J=2.0Hz) 7.43(1H, d, J=8.4Hz) 7.58(1H, dd, J=8.4Hz, 2.0Hz) 8.06(1H, d, J=2.0Hz)	
307	CN			196-198	44	446(MH⁺)	δ(DMSO-d_6) : 1.35-1.50(2H, m), 1.79-1.86(2H, m) 2.50-2.55(1H, m), 2.99-3.08(2H, m) 3.30(3H, s), 4.54-4.62(2H, m) 4.81(2H, s), 5.98(2H, s) 6.82(1H, dd, J=8.0Hz, 1.6Hz) 6.87(1H, d, J=8.0Hz) 6.92(1H, d, J=1.6Hz) 7.33(1H, d, J=2.4Hz) 7.71(1H, dd, J=8.4Hz, 1.6Hz) 8.27(1H, d, J=1.6Hz)	

Table 9



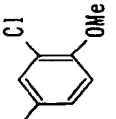
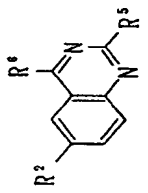
Ex.	R^2	R^5	R^1	m.p. (°C)	yield (%)	Mass	NMR	note
308	Cl			180-181	99	420(M+1)	δ(DMSO-d_6) : 1.97(2H, quintet, J=7.4Hz) 2.26(2H, t, J=7.4Hz) 2.72(2H, t, J=7.4Hz) 3.82(3H, s), 4.67(2H, d, J=5.7Hz) 7.08(1H, d, J=8.6Hz) 7.34(1H, dd, J=8.6Hz, 2.2Hz) 7.47(1H, d, J=2.2Hz) 7.64(1H, d, J=9.0Hz) 7.74(1H, dd, J=9.0Hz, 2.4Hz) 8.37(1H, d, J=2.4Hz) 8.76(1H, t, J=5.7Hz)	
309	Cl			> 250	17	393(MH+)	δ(DMSO-d_6) : 1.28-1.88(10H, m), 2.46-2.48(1H, m) 2.91-3.01(2H, m), 3.35-3.42(4H, m) 4.39(1H, brs), 4.57-4.63(2H, m) 7.22(1H, d, J=8.8Hz) 7.43(1H, dd, J=8.8Hz, 2.4Hz) 8.11(1H, brt, J=4.0Hz) 8.15(1H, d, J=2.4Hz)	

Table 10

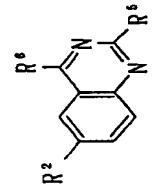


Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
310	Cl			> 250	100	361(MH+)	δ (DMSO) ; 0.23-0.29(2H, m), 0.41-0.48(2H, m) 1.11-1.22(1H, m), 1.40-1.52(2H, m) 1.81-1.87(2H, m), 2.45-2.52(1H, m) 2.93-3.01(2H, m), 3.26-3.35(2H, m) 4.60-4.67(2H, m) 7.25(1H, d, J=9.2Hz) 7.47(1H, dd, J=9.2Hz, 2.4Hz) 8.14(1H, m), 8.16(1H, d, J=2.4Hz) 12.18(1H, brs)	
311	Cl	Cl		172-174	43	326(M+1)	δ (DMSO-d_6) ; 1.75(2H, m), 1.98(2H, m), 2.64(1H, m) 3.39(2H, m), 4.23(2H, brd, J=13.2Hz) 7.71(1H, d, J=8.8Hz) 7.84(1H, dd, J=8.8Hz, 2.0Hz) 7.93(1H, d, J=2.0Hz)	

Table 11

Ex.	R²	R⁵	R⁶	m.p. (°C)	yield (%)	Mass	NMR	note
312	Cl			260-262	91	419(M+1)	δ (DMSO-d₆) ; 1.60(2H, m), 1.74(2H, m) 1.97(4H, brt, J=15.2Hz), 2.68(2H, m) 3.32(2H, t, J=11.6Hz) 3.53(2H, t, J=11.6Hz) 4.36(2H, d, J=13.6Hz) 4.57(2H, d, J=13.2Hz) 7.82(1H, d, J=9.2Hz) 7.86(1H, s), 8.18(1H, d, J=9.2Hz) 13.0(1H, brs)	hydrochloride
313	Cl			159-160	56	469(M+1)⁺	δ (DMSO-d₆) ; 1.21(3H, t, J=7.2Hz), 1.75(2H, brm) 1.95(2H, brm), 2.65(1H, m) 3.14(2H, brm), 4.00(2H, brm) 4.10(2H, q, J=7.2Hz) 4.43(2H, d, J=6.0Hz), 5.94(2H, s) 6.80(2H, brs), 6.91(1H, brs) 7.34(1H, brd, J=9.2Hz) 7.43(1H, brs) 7.51(1H, dd, J=9.2Hz, 2.4Hz) 7.62(1H, d, J=2.4Hz)	

Table 12



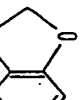
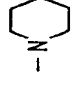
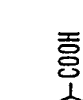
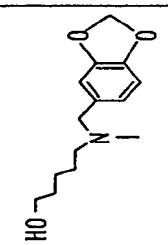
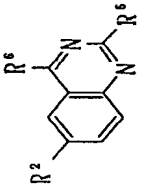
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
314	Cl			238-239 (decomp)	68	441(M+1)$^+$	δ (DMSO-d_6) : 1.75(2H, brm), 1.94(2H, brm) 2.56(1H, m), 3.14(2H, brm) 3.99(2H, brm), 4.43(2H, d, J=6.4Hz) 5.94(2H, s), 6.81(2H, brs) 6.91(1H, brs), 7.34(1H, brd, J=8.8Hz) 7.43(1H, brs) 7.51(1H, dd, J=8.8Hz, 2.4Hz) 7.62(1H, d, J=2.4Hz)	
315	Cl			170 (decomp)	68	527(MH$^+$)	δ (DMSO) : 1.22-1.33(2H, m), 1.36-1.51(4H, m) 1.69-1.82(4H, m), 2.25-2.81(1H, m) 2.97-3.06(2H, m), 3.32-3.52(4H, m) 4.29-4.52(3H, m), 4.72(2H, brs) 5.98(2H, s), 6.80-6.92(2H, m) 7.29(1H, d, J=9.2Hz), 7.45(1H, dd, J=9.2Hz, 1.2Hz) 7.60(1H, d, J=1.2Hz)	

Table 1 3



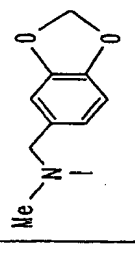
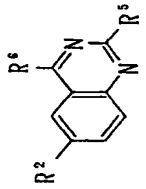
Ex.	R²	R⁵	R⁶	m.p. (°C)	yield (%)	Mass	NMR	note
316	CN			oily substance	quantitative	474(MH⁺)	δ (CDCl₃) ; 1.26(3H, t, J=7.2Hz) 1.66-1.77(2H, m), 1.93-2.01(2H, m) 2.51-2.62(1H, m), 3.09-3.13(2H, m) 3.23(3H, s), 4.14(2H, q, J=7.2Hz) 4.74-4.80(2H, m), 4.79(2H, s) 5.98(2H, s), 6.80-6.84(3H, m) 7.42(1H, d, J=8.8Hz) 7.57(1H, dd, J=8.8Hz, 2.0Hz), 8.05(1H, d, J=2.0Hz)	

Table 14



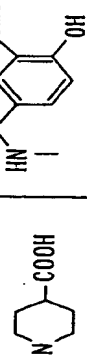
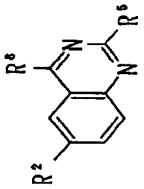
Ex.	R²	R⁵	R⁶	m.p. (°C)	yield (%)	Mass	NMR	note
317	Cl			244-245	quantitative	443(M+1)⁺	δ (DMSO-d₆) : 1.49(2H, m), 1.88(2H, m), 2.53(1H, m) 3.08(2H, m), 3.74(3H, s) 4.58(2H, d, J=5.2Hz), 4.61(2H, m) 6.71(1H, d, J=8.0Hz) 6.80(1H, dd, J=8.0Hz, 2.0Hz), 6.99(1H, d, J=2.0Hz), 7.38(1H, brs) 7.56(1H, brs), 8.25(1H, brs) 8.86(1H, s), 12.19(1H, brs)	
318	Cl			254-255 (decomp.)	92	443(M+1)⁺	δ (DMSO-d₆) : 1.48(2H, m), 1.88(2H, m), 2.54(1H, m) 3.10(2H, m), 3.72(3H, s), 4.54(2H, m) 4.56(2H, d, J=5.6Hz) 6.77(1H, dd, J=8.0Hz, 2.0Hz) 6.82(1H, d, J=2.0Hz) 6.84(1H, d, J=8.0Hz) 7.45(1H, brs), 7.60(1H, brs) 8.28(1H, brs), 8.90(1H, s) 12.21(1H, brs)	

Table 15



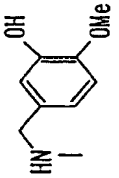
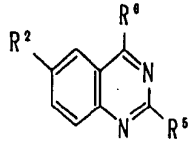
Ex.	R^2	R^5	R^8	m.p. (°C)	yield (%)	Mass	NMR	note
319	Cl	Cl		193-194	58	350(M+1)$^+$	δ (DMSO-d_6) : 3.71(3H, s), 4.57(2H, d, J=5.6Hz) 6.74(1H, dd, J=8.4Hz, 2.0Hz) 6.77(1H, d, J=2.0Hz) 6.84(1H, d, J=8.4Hz) 7.62(1H, d, J=8.8Hz) 7.79(1H, dd, J=8.8Hz, 2.4Hz) 8.46(1H, d, J=2.4Hz) 8.91(1H, s), 9.22(1H, t, J=5.6Hz)	

Table 16



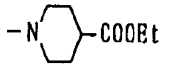
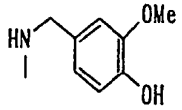
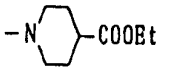
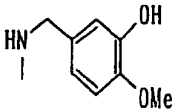
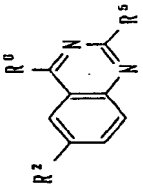
Ex.	R^2	R^5	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
320	Cl			173-174	78	471(M+1)$^+$	δ(CDCl$_3$) : 1.26(3H, t, J=7.2Hz), 1.72(2H, m) 1.98(2H, m), 2.56(1H, m), 3.05(2H, m) 3.88(3H, s), 4.15(2H, q, J=7.2Hz) 4.68(2H, d, J=5.2Hz), 4.82(2H, m) 5.56(1H, t, J=5.2Hz), 5.65(1H, brs) 6.90(3H, m), 7.39(1H, d, J=8.8Hz) 7.42(1H, d, J=2.4Hz) 7.44(1H, dd, J=8.8Hz, 2.4Hz)	
321	Cl			170-171	91	471(M+1)$^+$	δ(CDCl$_3$) : 1.26(3H, t, J=7.2Hz), 1.72(2H, m) 1.97(2H, m), 2.55(1H, m), 3.04(1H, m) 3.90(3H, s), 4.15(2H, q, J=7.2Hz) 4.66(2H, d, J=5.2Hz), 4.80(2H, m) 5.57(1H, t, J=5.2Hz), 5.68(1H, brs) 6.83(1H, d, J=8.0Hz) 6.87(1H, dd, J=8.0Hz, 2.0Hz) 6.97(1H, d, J=2.0Hz), 7.38(1H, d, J=8.8Hz) 7.41(1H, d, J=2.4Hz) 7.43(1H, dd, J=8.8Hz, 2.4Hz)	

Table 17

Ex.	R^2	R^5	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
322	Cl			>260	99	476(M+1)$^+$	δ (DMSO-d_6) ; 1.53(2H,m), 1.90(2H,m), 2.62(1H,m) 3.29(2H,m), 4.41(2H,m) 4.83(2H,d,J=5.6Hz) 7.74(1H,d,J=8.4Hz) 7.76(1H,dd,J=8.4Hz,2.0Hz) 7.85(1H,d,J=8.4Hz) 7.90(1H,d,J=8.4Hz) 8.15(1H,d,J=2.0Hz), 8.51(1H,s) 10.34(1H,brs), 12.28(1H,brs)	hydro-chlo-ride
323	Cl			>260	65	446(M+1)$^+$	δ (DMSO-d_6) ; 1.58(2H,m), 1.95(2H,m), 2.63(1H,m) 3.32(2H,m), 4.45(2H,m) 4.62(2H,d,J=5.2Hz), 5.33(2H,brs) 6.58(1H,dd,J=8.0Hz,2.0Hz) 6.79(1H,d,J=2.0Hz) 7.13(1H,d,J=8.0Hz) 7.85(1H,d,J=8.8Hz) 7.89(1H,d,J=8.8Hz) 8.51(1H,s), 10.14(1H,brs) 12.22(1H,brs)	hydro-chlo-ride

Table 18



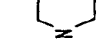
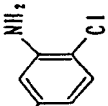
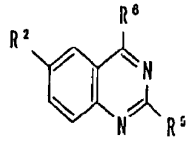
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
324	Cl			218-219 (decomp)	25	476(M+1)$^+$	δ (DMSO-d_6) : 1.20(3H, t, J=7.2Hz), 1.57(2H, m) 1.96(2H, m), 2.73(1H, m), 3.31(2H, m) 4.08(2H, q, J=7.2Hz), 4.49(2H, m) 4.61(2H, d, J=5.6Hz) 6.59(1H, dd, J=8.0Hz, 2.0Hz) 6.79(1H, d, J=2.0Hz) 7.13(1H, d, J=8.0Hz) 7.85(1H, dd, J=9.2Hz, 2.4Hz) 7.93(1H, d, J=9.2Hz) 8.53(1H, d, J=2.4Hz) 10.19(1H, brt, J=5.6Hz) 12.31(1H, brs)	
325	Cl	Cl		186-187	77	350(M+1)$^+$	δ (DMSO-d_6) : 3.74(3H, s), 4.58(2H, d, J=5.6Hz) 6.70(1H, d, J=8.0Hz) 6.75(1H, d, J=8.0Hz, 1.6Hz) 7.00(1H, d, J=1.6Hz) 7.61(1H, d, J=8.8Hz) 7.78(1H, dd, J=8.8Hz, 2.4Hz) 8.46(1H, d, J=2.4Hz), 8.87(1H, s) 8.19(1H, t, J=5.6Hz)	

Table 19



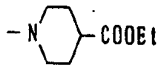
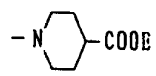
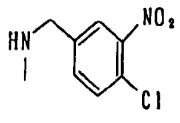
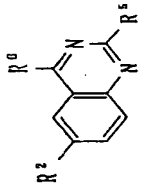
Ex.	R^2	R^5	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
326	Cl			175-176	76	475(M+1)$^+$	δ (DMSO-d_6) ; 1.198(3H, t, J=7.2Hz) 1.203(3H, t, J=7.2Hz), 1.65(2H, m) 1.78(2H, m), 2.01(4H, m), 2.76(1H, m) 2.82(1H, m), 3.31(2H, m), 3.55(2H, m) 4.09(2H, q, J=7.2Hz) 4.10(2H, q, J=7.2Hz), 4.41(2H, m) 4.53(2H, m) 7.84(1H, dd, J=8.8Hz, 1.6Hz) 7.90(1H, d, J=1.6Hz) 8.00(1H, d, J=8.8Hz)	hydro-chlo-ride
327	Cl	Cl		220-221	71	383(M+1)$^+$	δ (DMSO-d_6) ; 4.81(2H, d, J=5.6Hz) 7.67(1H, d, J=8.4Hz) 7.71(1H, dd, J=8.4Hz, 2.0Hz) 7.74(1H, d, J=8.4Hz) 7.84(1H, dd, J=8.4Hz, 2.0Hz) 8.11(1H, d, J=2.0Hz) 8.44(1H, d, J=2.0Hz) 9.39(1H, t, J=5.6Hz)	

Table 20



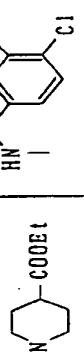
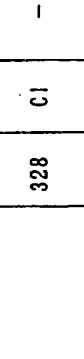
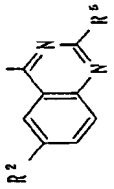
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
328	Cl			230-231	73	504(M+1)$^+$	δ (DMSO-d_6) ; 1.20(3H, t, J=7.2Hz), 1.51(2H, m) 1.89(2H, m), 2.72(1H, m), 3.27(2H, m) 4.08(2H, q, J=7.2Hz), 4.44(2H, m) 4.82(2H, d, J=5.6Hz) 7.73(1H, d, J=8.4Hz) 7.76(1H, dd, J=8.4Hz, 2.0Hz) 7.85(1H, dd, J=8.8Hz, 2.0Hz) 7.92(1H, d, J=8.8Hz) 8.14(1H, d, J=2.0Hz) 8.52(1H, d, J=2.0Hz), 10.35(1H, brs) 12.35(1H, brs)	hydro-chlo-ride
329	Cl			>260	65	446(M+1)$^+$	δ (DMSO-d_6) ; 1.58(2H, m), 1.95(2H, m), 2.63(1H, m) 3.32(2H, m), 4.45(2H, m) 4.62(2H, d, J=5.2Hz), 5.33(2H, brs) 6.58(1H, dd, J=8.0Hz, 2.0Hz) 6.79(1H, d, J=2.0Hz) 7.13(1H, d, J=8.0Hz) 7.85(1H, d, J=8.8Hz) 7.89(1H, d, J=8.8Hz), 8.51(1H, s) 10.14(1H, brs), 12.22(1H, brs)	hydro-chlo-ride

Table 21



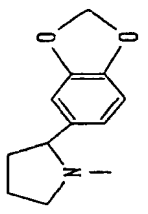
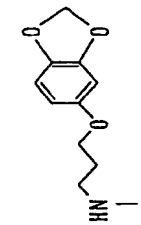
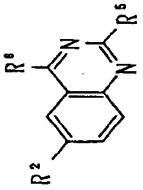
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
330	OMe	H		oily substance	85		δ (CDCl$_3$) : 1.95-2.10(3H,m), 2.37(1H,m) 3.58(3H,s), 4.05-4.20(2H,m) 5.58(1H,m), 5.93(1H,s), 5.94(1H,s) 6.78(1H,d,J=8.4Hz), 6.84(1H,s) 6.85(1H,d,J=8.4Hz) 7.30(1H,d,J=10.0Hz), 7.35(1H,s) 7.74(1H,d,J=10.0Hz), 8.53(1H,s)	
331	Cl			139-140	83	485(M+1)$^+$	δ (DMSO-d$_6$) : 1.44(2H,m), 1.82(2H,m), 2.03(2H,m) 2.46(1H,m), 2.94(2H,m), 3.59(2H,m) 3.96(2H,t,J=6.0Hz), 4.62(2H,m) 5.91(2H,s) 6.32(1H,dd,J=8.4Hz,2.4Hz) 6.56(1H,d,J=2.4Hz) 6.75(1H,d,J=8.4Hz) 7.22(1H,d,J=8.8Hz) 7.44(1H,dd,J=8.8Hz,2.4Hz) 8.05(1H,brt), 8.08(1H,d,J=2.4Hz) 12.14(1H,brs)	

Table 22



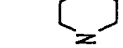
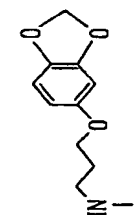
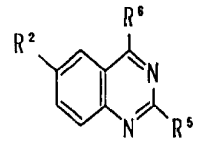
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
332	Cl			184-185	97	513(M+1)$^+$	δ (DMSO-d_6) : 1.18(3H, t, J=7.2Hz), 1.59(2H, m) 1.95(2H, m), 2.05(2H, m), 2.72(1H, m) 3.3(2H, m), 3.71(2H, m) 3.98(2H, t, J=6.0Hz) 4.07(2H, q, J=7.2Hz), 4.48(2H, m) 5.91(2H, s) 6.29(1H, dd, J=8.4Hz, 2.4Hz) 6.52(1H, d, J=2.4Hz) 6.74(1H, d, J=8.4Hz), 7.81(2H, brs) 8.41(1H, brs), 9.59(1H, brs) 12.07(1H, brs)	hydrochloride
333	Cl	Cl		148-149	87	392(M+1)$^+$	δ ($CDCl_3$) : 2.21(2H, m), 3.88(2H, m) 4.16(2H, t, J=5.4Hz), 5.94(2H, s) 6.39(1H, dd, J=8.4Hz, 2.8Hz) 6.56(1H, d, J=2.8Hz), 6.72(1H, brs) 6.74(1H, d, J=8.4Hz) 7.63(1H, d, J=2.0Hz) 7.66(1H, dd, J=8.8Hz, 2.0Hz) 7.70(1H, d, J=8.8Hz)	

Table 2 3



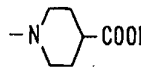
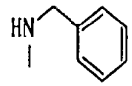
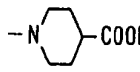
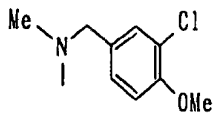
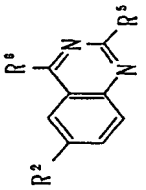
Ex.	R^2	R^5	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
334	Cl			240-241 (decomp)	60	397(M+1)$^+$	δ(DMSO-d_6) : 1.39(2H, m), 1.80(2H, m), 2.47(1H, m) 2.96(2H, m), 4.57(2H, m) 4.66(2H, d, J=5.6Hz) 7.15-7.45(6H, m) 7.48(1H, dd, J=9.2Hz, 1.6Hz) 8.17(1H, d, J=1.6Hz), 8.64(1H, brs) 12.15(1H, brs)	
335	CN			176-177	40	466(MH$^+$)	δ($CDCl_3$) : 1.62-1.79(2H, m), 1.96-2.03(2H, m) 1.57-1.64(1H, m), 3.08-3.18(2H, m) 3.25(3H, s), 3.91(3H, s) 4.70-4.79(2H, m), 4.80(2H, s) 6.93(1H, d, J=8.4Hz) 7.19(1H, dd, J=8.4Hz, 2.0Hz) 7.36(1H, d, J=2.0Hz) 7.45(1H, d, J=8.8Hz) 7.58(1H, dd, J=8.8Hz, 2.0Hz) 8.06(1H, d, J=2.0Hz)	

Table 24



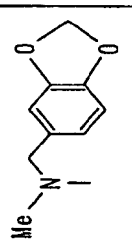
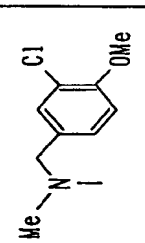
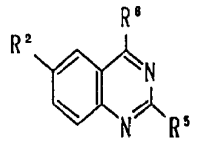
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
336	CN	Cl		156-158	89	353(MH^+)	δ (DMSO-d_6) ; 3.42(3H, s), 4.93(2H, s), 5.99(2H, s) 6.86(1H, dd, J=8.0Hz, 1.6Hz) 6.90(1H, d, J=8.0Hz) 6.98(1H, d, J=1.6Hz) 7.73(1H, d, J=8.4Hz) 8.08(1H, dd, J=8.4Hz, 2.0Hz) 8.63(1H, d, J=2.0Hz)	
337	CN	Cl		173-175	86	373(MH^+)	δ (DMSO-d_6) ; 3.44(3H, s), 3.83(3H, s), 4.95(2H, s) 7.13(1H, d, J=8.8Hz) 7.34(1H, dd, J=8.8Hz, 2.4Hz) 7.50(1H, d, J=2.4Hz) 7.74(1H, d, J=8.8Hz) 8.08(1H, dd, J=8.8Hz, 1.6Hz) 8.65(1H, d, J=1.6Hz)	

Table 25



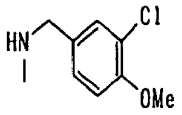
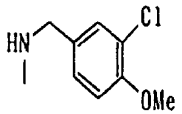
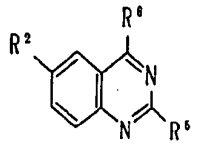
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
338	Cl	−COOH		187-188	93	378(M+1)$^+$	δ(DMSO-d_6) ; 3.83(3H, s), 4.75(2H, d, J=5.6Hz) 7.10(1H, d, J=8.4Hz) 7.38(1H, dd, J=8.4Hz, 2.4Hz) 7.53(1H, d, J=2.4Hz) 7.84(1H, d, J=8.8Hz) 7.88(1H, dd, J=8.8Hz, 2.0Hz) 8.50(1H, d, J=2.0Hz) 9.15(1H, brt, J=5.6Hz)	
339	Cl			180-181	99	420(M+1)$^+$	δ(DMSO-d_6) ; 1.97(2H, quintet, J=7.4Hz) 2.26(2H, t, J=7.4Hz) 2.72(2H, t, J=7.4Hz), 3.82(3H, s) 4.67(2H, d, J=5.7Hz) 7.08(1H, d, J=8.6Hz) 7.34(1H, dd, J=8.6Hz, 2.2Hz) 7.47(1H, d, J=2.2Hz) 7.64(1H, d, J=9.0Hz) 7.74(1H, dd, J=9.0Hz, 2.4Hz) 8.37(1H, d, J=2.4Hz) 8.76(1H, t, J=5.7Hz)	

Table 26



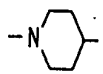
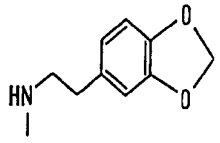
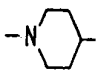
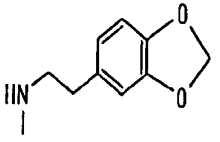
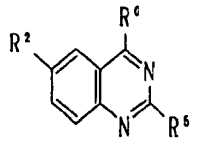
Ex.	R^2	R^5	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
340	Cl			173-174	88	483(M+1)$^+$	δ (DMSO-d_6) : 1.20(3H, t, J=7.2Hz), 1.67(2H, m) 2.01(2H, m), 2.77(1H, m) 2.89(2H, t, J=7.2Hz), 3.39(2H, m) 3.75(2H, m), 4.10(2H, q, J=7.2Hz) 4.56(2H, m), 5.96(2H, s) 6.69(1H, dd, J=8.0Hz, 1.6Hz) 6.80(1H, d, J=8.0Hz) 6.86(1H, d, J=1.6Hz) 7.83(1H, dd, J=8.8Hz, 2.4Hz) 7.95(1H, d, J=8.8Hz) 8.44(1H, d, J=2.4Hz), 9.69(1H, brs) 12.34(1H, brs)	hydrochloride
341	Cl			186-187	75	455(M+1)$^+$	δ (DMSO-d_6) : 1.50(2H, m), 1.88(2H, m), 2.52(1H, m) 2.86(2H, t, J=7.4Hz), 3.03(2H, m) 3.63(2H, m), 4.65(2H, m), 5.96(2H, s) 6.69(1H, d, J=8.0Hz) 6.82(1H, d, J=8.0Hz), 6.83(1H, s) 7.27(1H, d, J=9.2Hz) 7.48(1H, dd, J=9.2Hz, 2.4Hz) 8.10(1H, d, J=2.4Hz), 8.17(1H, brs) 12.19(1H, brs)	

Table 27



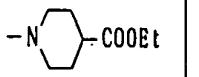
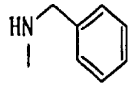
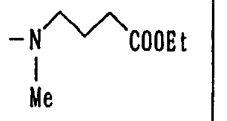
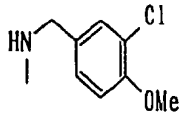
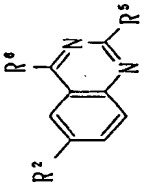
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
342	Cl			166-167	95	425(M+1)$^+$	δ (DMSO-d_6) ; 1.19(3H, t, J=7.2Hz), 1.57(2H, m) 1.94(2H, m), 2.73(1H, m), 3.31(2H, m) 4.08(2H, q, J=7.2Hz), 4.48(2H, m) 4.77(2H, d, J=5.6Hz) 7.25-7.45(5H, m), 7.85(2H, s) 8.52(1H, s), 10.19(1H, brs) 12.19(1H, brs)	hydro-chlo-ride
343	Cl			212-213	41	477(M+1)$^+$	δ (DMSO-d_6) ; 1.12(3H, t, J=7.2Hz), 1.80(2H, brs) 2.23(2H, brs), 3.24(3H, s) 3.73(2H, brs), 3.82(3H, s) 3.99(2H, q, J=7.2Hz) 4.71(2H, d, J=6.0Hz) 7.09(1H, d, J=8.8Hz) 7.35(1H, d, J=8.4Hz), 7.48(1H, s)	hydro-chlo-ride

Table 28



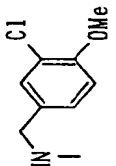
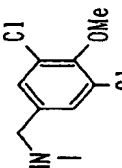
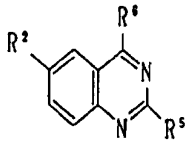
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
344	Cl			140-141	81	449(M+1)$^+$	δ (DMSO-d_6) : 1.74(2H, brm), 1.59(2H, brm) 3.10(3H, s), 3.61(2H, t, J=7.2Hz) 3.81(3H, s), 4.61(2H, d, J=5.6Hz) 7.07(1H, d, J=8.4Hz) 7.31(1H, dd, J=8.4Hz, 2.0Hz) 7.36(1H, brs), 7.43(1H, d, J=2.0Hz) 7.55(1H, brs), 8.20(1H, brs) 12.03(1H, brs)	
345	CN	Cl		248-249	78	393(M+1)$^+$	δ (DMSO-d_6) : 3.81(3H, s), 4.71(2H, d, J=5.6Hz) 7.55(2H, s), 7.76(1H, d, J=8.4Hz) 8.14(1H, dd, J=8.4Hz, 2.0Hz) 8.88(1H, d, J=2.0Hz) 9.49(1H, brt, J=5.6Hz)	

Table 2 9



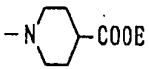
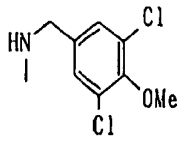
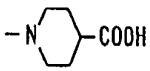
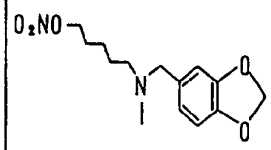
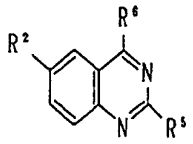
Ex.	R^2	R^5	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
346	CN			207-208	82	514(M+1)$^+$	δ(DMSO-d_6) : 1.17(3H, t, J=7.2Hz), 1.36(2H, brm) 1.82(2H, brm), 2.62(1H, m) 3.03(2H, m), 3.78(3H, s) 4.05(2H, q, J=7.2Hz) 4.59(2H, brd, J=5.6Hz) 4.63(2H, brm), 7.29(1H, d, J=8.8Hz) 7.50(2H, s) 7.75(1H, dd, J=8.8Hz, 2.0Hz) 8.53(1H, d, J=2.0Hz) 8.86(1H, brt, J=5.6Hz)	
347	Cl			amorphous	19	572(MH$^+$)	δ($CDCl_3$) : 1.25-2.02(12H, m), 2.47-2.57(1H, m) 3.02-3.18(2H, m), 3.50-3.58(2H, m) 4.42(2H, t, J=6.6Hz) 4.63-4.74(2H, m), 4.75(2H, s) 5.47(2H, s), 6.80-6.81(3H, m) 7.41(1H, dd, J=8.0Hz, 2.0Hz) 7.50(1H, d, J=8.0Hz) 7.62(1H, d, J=2.0Hz)	

Table 30



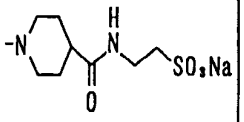
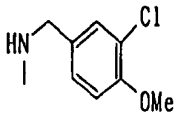
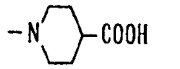
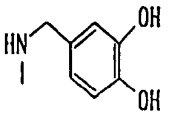
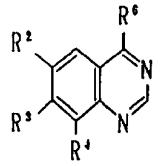
Ex.	R^2	R^5	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
348	NC			> 250	62		δ (DMSO-d_6) ; 1.40(2H, m), 1.72(2H, m), 2.34(1H, m) 2.54(2H, t, J=7.2Hz), 2.89(2H, m) 3.31(2H, m), 3.82(3H, s) 4.59(2H, d, J=5.6Hz), 4.78(2H, m) 7.09(1H, d, J=8.4Hz) 7.28(1H, d, J=8.4Hz) 7.32(1H, dd, J=8.4Hz, 2.0Hz) 7.45(1H, d, J=2.0Hz) 7.72(1H, dd, J=8.4Hz, 2.0Hz) 7.74(1H, t, J=5.6Hz) 8.54(1H, d, J=2.0Hz) 8.77(1H, t, J=5.6Hz)	
349	Cl			216-218 (decomp.)	95	429(MH^+)	δ (DMSO-d_6) ; 1.38-1.47(2H, m), 1.80-1.84(2H, m) 2.44-2.49(1H, m), 2.93-3.00(2H, m) 4.48(2H, d, J=5.6Hz) 4.57-4.61(2H, m), 6.60-6.65(2H, m) 6.74(1H, d, J=1.6Hz) 7.24(1H, d, J=8.8Hz) 7.46(1H, dd, J=8.8Hz, 2.0Hz) 8.15(1H, d, J=2.0Hz), 8.48(1H, brs) 8.675(1H, s), 8.75(1H, s) 12.14(1H, brs)	

Table 3 1



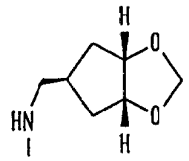
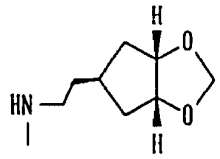
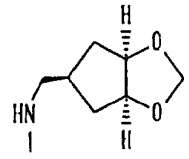
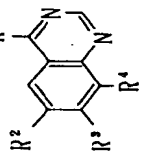
Ex.	R^2	R^3	R^4	R^6	m.p. (℃)	yield (%)	Mass	NMR	note
350	MeO	MeO	MeO		163-164	70	362(M+1)$^+$	δ(CDCl$_3$) : 1.41(2H,m), 2.16(2H,m), 2.60(1H,m) 3.69(2H,m), 4.02(3H,s), 4.03(3H,s) 4.11(3H,s), 4.55(2H,m), 4.63(1H,s) 5.06(1H,s), 5.75(1H,brs) 6.83(1H,brs), 8.59(1H,s)	
351	MeO	MeO	MeO		173-174	37	376(M+1)$^+$	δ(CDCl$_3$) : 1.86(2H,m), 1.79(2H,m) 2.14(2H,dd,J=14.4Hz,5.6Hz) 2.27(1H,m), 3.68(2H,m), 3.99(3H,s) 4.02(3H,s), 4.11(3H,s), 4.50(2H,m) 4.62(1H,s), 5.03(1H,s), 5.78(1H,brs) 6.76(1H,s), 8.60(1H,s)	
352	MeO	MeO	MeO		170-171	70	362(M+1)$^+$	δ(CDCl$_3$) : 1.87(2H,m), 1.99(2H,m), 2.63(1H,m) 3.73(2H,m), 4.00(3H,s), 4.03(3H,s) 4.11(3H,s), 4.58(2H,m), 4.80(1H,s) 5.17(1H,s), 6.14(1H,brs), 6.80(1H,s) 8.59(1H,s)	

Table 3 2



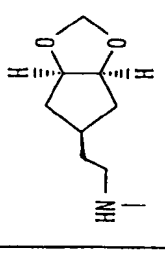
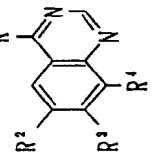
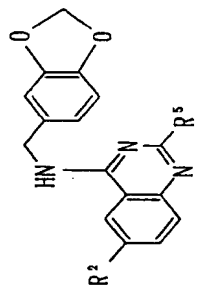
Ex.	R²	R³	R⁴	R⁶	m.p. (°C)	yield (%)	Mass	NMR	note
353	MeO	MeO	MeO		143-144	24	376(M+1)⁺	δ (CDCl₃) : 1.77(2H, m), 1.80(2H, m), 1.97(2H, m) 2.07(1H, m), 3.64(2H, m), 3.98(3H, s) 4.03(3H, s), 4.10(3H, s), 4.58(2H, m) 4.83(1H, s), 5.12(1H, s), 6.24(1H, brs) 6.92(1H, s), 8.60(1H, s)	
354	MeO	MeO	MeO		139-140	88	303(M+1)⁺	δ (CDCl₃) : 2.16(2H, quintet, J=6.8Hz) 2.52(1H, t, J=6.8Hz) 3.85(2H, dt, J=6.8Hz, 6.0Hz) 3.99(3H, s), 4.03(3H, s), 4.10(3H, s) 6.29(1H, brs), 6.90(1H, s), 8.60(1H, s)	
355	MeO	MeO	MeO		160-161	94	317(M+1)⁺	δ (CDCl₃) : 1.81(2H, m), 1.94(2H, m) 2.47(2H, t, J=6.8Hz) 3.75(2H, dt, J=6.8Hz, 6.0Hz) 4.00(3H, s), 4.03(3H, s), 4.11(3H, s) 5.91(1H, brs), 6.82(1H, s), 8.60(1H, s)	

Table 33



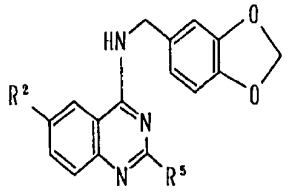
Ex.	R^2	R^3	R^4	R^6	m.p. (°C)	yield (%)	Mass	NMR	note
356	MeO	MeO	MeO		155-156	75	331(M+1)$^+$	δ (CDCl$_3$) : 1.6-1.8(6H, m), 2.40(2H, t, J=7.0Hz) 3.70(2H, dt, J=7.0Hz, 5.6Hz) 4.00(3H, s), 4.03(3H, s), 4.11(3H, s) 6.00(1H, brs), 6.84(1H, s), 8.60(1H, s)	

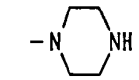
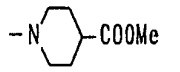
Table 34



Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
357	Cl		225-227	85	483(M+1)	δ (DMSO-d_6) : 0.93(2H, m), 1.18(2H, m), 1.44(1H, m) 1.51(2H, m), 1.64(2H, brd, J=12.0Hz) 2.18(2H, t, J=7.6Hz), 2.75(2H, brt, J=12.0Hz) 4.53(2H, d, J=5.6Hz), 4.73(2H, brd, J=12.8Hz) 5.94(1H, s), 6.83(2H, s), 6.93(1H, s) 7.22(1H, d, J=8.8Hz) 7.45(1H, dd, J=8.8Hz, 2.4Hz) 8.11(1H, d, J=2.4Hz), 8.50(1H, t, J=5.6Hz)	
358	Cl		190-192 (decomp.)	32	490(MH+)	δ (DMSO-d_6) : 1.90-1.95(2H, m), 3.82(2H, t, J=6.4Hz) 4.28(2H, t, J=6.8Hz), 4.61(2H, d, J=5.6Hz) 5.95(2H, s), 6.04(2H, s), 6.13(1H, s) 7.50(1H, d, J=8.8Hz) 7.64(1H, dd, J=8.8Hz, 2.4Hz) 8.54(1H, d, J=2.4Hz), 8.75(1H, t, J=1.6Hz)	

Table 3 5



Ex.	R^2	R^5	m.p. (℃)	yield (%)	Mass	NMR	note
359	Cl		121-122	95	475(MH^+)	δ($CDCl_3$) : 1.42-1.59(4H, m), 1.70-1.89(4H, m), 4.43(4H, q, J=6.8Hz), 4.73(2H, d, J=4.4Hz) 5.95(2H, s), 6.28(1H, br) 6.77(1H, d, J=8.0Hz), 6.83(1H, d, J=8.0Hz) 6.85(1H, s), 7.54(1H, d, J=8.8Hz) 7.58(1H, d, J=8.8Hz), 7.66(1H, s)	
360	Cl		173-175	98	398(M+1)	δ($DMSO-d_6$) : 2.66(4H, t, J=4.8Hz), 3.66(1H, t, J=4.8Hz) 4.54(2H, d, J=6.0Hz), 5.94(2H, s) 6.83(2H, s), 6.92(1H, s), 7.22(1H, d, J=8.8Hz) 7.46(1H, dd, J=8.8Hz, 2.4Hz) 8.12(1H, d, J=2.4Hz), 8.51(1H, t, J=6.0Hz)	
361	Cl		233-234	93	455$(M+1)^+$	δ($DMSO-d_6$) : 1.58(2H, m), 1.95(2H, m), 2.75(1H, m) 3.3(2H, m), 3.61(3H, s), 4.46(2H, m) 4.65(2H, d, J=5.6Hz), 5.96(2H, s) 6.84(1H, d, J=8.0Hz) 6.87(1H, dd, J=8.0Hz, 1.2Hz) 6.97(1H, d, J=1.2Hz), 7.78(1H, brd, J=8.8Hz) 7.81(1H, brd, J=8.8Hz), 8.45(1H, brs) 10.05(1H, brs), 12.05(1H, brs)	hydrochloride

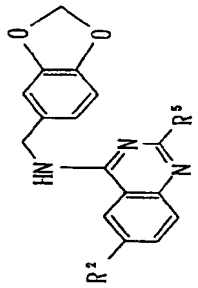


Table 3 6

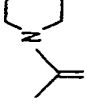
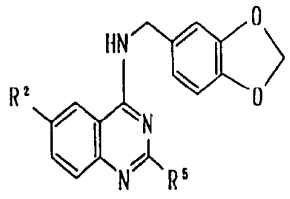
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
362	Cl			12		δ (DMSO-d_6) ; 1.48(2H, m), 1.64(1H, m), 1.85(1H, m) 2.36(1H, m), 2.96(2H, m), 3.28(1H, m) 4.19(1H, m), 4.64(2H, d, J=5.6Hz) 5.95(2H, s), 6.82(2H, s), 6.93(1H, s) 7.71(1H, brd), 7.79(1H, brd), 8.47(1H, s) 9.04(1H, brs)	
363	H	Cl	191-192	94	314(M+1)	δ ($CDCl_3$) ; 4.76(2H, d, J=5.2Hz), 5.97(2H, s) 6.15(1H, brs), 6.80(1H, d, J=8.0Hz) 6.87(1H, dd, J=8.0Hz, 1.6Hz) 6.89(1H, d, J=1.6Hz) 7.44(1H, ddd, J=8.0Hz, 6.8Hz, 1.6Hz) 7.66(1H, d, J=8.0Hz), 7.74(1H, t, J=6.8Hz) 7.78(1H, dd, J=6.8Hz, 1.6Hz)	

Table 37



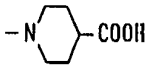
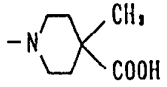
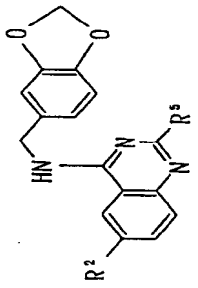
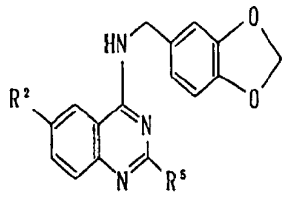
Ex.	R^2	R^5	m.p. (℃)	yield (%)	Mass	NMR	note
364	H		159-161	97	407(M+1)	δ (DMSO-d_6) : 1.38(2H, m), 1.79(2H, brd, J=12.8Hz) 2.47(1H, m), 2.94(2H, brt, J=11.2Hz) 4.56(2H, d, J=5.6Hz), 4.61(2H, m) 5.93(2H, s), 6.81(1H, d, J=8.0Hz) 6.84(1H, dd, J=8.0Hz, 1.6Hz) 6.93(1H, d, J=1.6Hz), 7.04(1H, t, J=8.4Hz) 7.24(1H, d, J=8.4Hz), 7.48(1H, t, J=8.4Hz) 7.98(1H, t, J=8.4Hz), 8.47(1H, brs) 12.13(1H, brs)	
365	Cl		243-245	81	455(M+1)	δ (DMSO-d_6) : 1.12(3H, s), 1.25(2H, m), 1.88(2H, m) 3.23(2H, m), 4.20(2H, m), 4.53(2H, d, J=6.0Hz) 5.94(2H, s), 6.83(2H, s), 6.92(1H, s) 7.23(1H, d, J=9.2Hz) 7.46(1H, dd, J=9.2Hz, 2.4Hz) 8.12(1H, d, J=2.4Hz), 8.53(1H, t, J=6.0Hz)	

Table 3 8



Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
366	Cl		174-175	99	484(M+1)	δ (DMSO-d_6) : 1.66(2H, quintet, J=7.2Hz) 2.24(2H, t, J=7.2Hz), 2.29(2H, t, J=7.2Hz) 2.35(4H, m), 3.72(4H, m), 4.55(2H, d, J=5.6Hz) 5.95(2H, s), 6.83(2H, s), 6.93(1H, s) 7.24(1H, d, J=8.8Hz) 7.47(1H, dd, J=8.8Hz, 2.4Hz) 8.14(1H, d, J=2.4Hz), 8.53(1H, t, J=5.6Hz)	
367	Cl		237-239 (decomp)	quantitative	412(M+1)+	δ (DMSO-d_6) : 2.79(3H, s), 3.14(2H, m), 3.54(2H, m) 3.62(2H, m), 4.71(2H, d, J=5.6Hz), 4.94(2H, m) 5.99(2H, s), 6.87(1H, d, J=8.0Hz) 6.94(1H, dd, J=8.0Hz, 1.6Hz) 7.03(1H, d, J=1.6Hz), 7.87(1H, brd) 8.07(1H, brs), 8.60(1H, brs), 10.29(1H, brs) 11.36(1H, brs), 13.13(1H, brs)	dihydro-chloride

Table 3 9



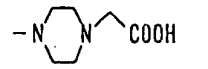
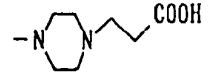
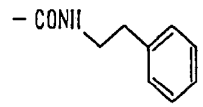
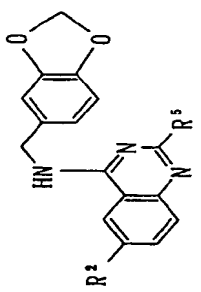
Ex.	R^2	R^5	m.p. (℃)	yield (%)	Mass	NMR	note
368	Cl		193-195	86	456(M+1)	δ(DMSO-d_6) ; 2.53(4H, m), 3.00(2H, brs), 3.75(4H, m) 4.53(2H, brd, J=6.0Hz), 5.94(2H, s) 6.82(2H, brs), 6.92(1H, s) 7.23(1H, d, J=8.8Hz), 7.47(1H, brd, J=8.8Hz) 8.14(1H, brs), 8.55(1H, t, J=6.0Hz)	
369	Cl		174-176	90	470(M+1)	δ(DMSO-d_6) ; 2.39(6H, m), 2.56(2H, t, J=7.2Hz) 3.71(2H, brs), 4.55(2H, d, J=5.6Hz) 1.83(2H, s), 6.93(1H, s), 7.24(1H, d, J=8.8Hz) 7.48(1H, dd, J=8.8Hz, 2.4Hz) 8.14(1H, d, J=2.4Hz), 8.55(1H, t, J=5.6Hz)	
370	Cl		166-169 (decomp)	80	461(MH^+)	δ(DMSO-d_6) ; 2.86(2H, t, J=7.2Hz), 3.53(2H, q, J=8.0Hz) 4.74(2H, d, J=5.2Hz), 5.97(2H, s) 6.86-6.89(2H, m), 7.01(1H, d, J=1.2Hz) 7.18-7.32(5H, m), 7.83(1H, d, J=8.8Hz) 7.86(2H, dd, J=8.8Hz, 2.0Hz) 8.50(1H, d, J=2.0Hz), 8.70(1H, brt, J=5.2Hz) 9.02(1H, brt, J=5.0Hz)	

Table 40



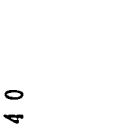
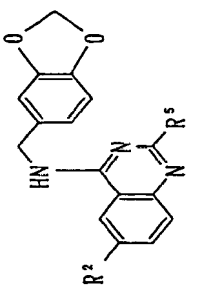
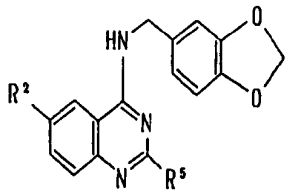
Ex.	R²	R⁵	m.p. (°C)	yield (%)	Mass	NMR	note
371	Cl		223-225 (decomp)	42	401(MH⁺)	δ (DMSO-d₆) ; 3.37(2H, q, J=6.0Hz), 3.53(2H, q, J=5.8Hz) 4.75(2H, d, J=6.0Hz), 4.82(1H, t, J=5.4Hz) 5.97(2H, s), 6.86(1H, d, J=8.0Hz) 6.94(1H, dd, J=8.0Hz, 1.6Hz) 7.04(1H, d, J=1.6Hz), 7.81-7.88(2H, m) 8.50(1H, d, J=2.0Hz), 8.64(1H, t, J=6.0Hz) 9.04(1H, t, J=6.0Hz)	
372	Cl		199-201 (decomp)		424(MH⁺)	δ (DMSO-d₆) ; 0.99(3H, t, J=7.4Hz), 1.79-1.84(2H, m) 4.41(2H, t, J=6.6Hz), 4.83(2H, d, J=5.6Hz) 5.97(2H, s), 6.85(1H, d, J=28.0Hz) 6.93(1H, dd, J=8.0Hz, 1.6Hz) 7.03(1H, d, J=1.6Hz), 7.87(1H, d, J=8.8Hz) 7.91(1H, dd, J=8.8Hz, 2.2Hz) 8.56(1H, d, J=2.2Hz), 8.727(1H, brt, J=5.6Hz)	

Table 41



Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
373	Br	Cl	213-214	80	392(M+1)+	δ (DMSO-d_6) ; 4.63(2H, d, J=5.6Hz), 5.99(2H, s), 6.87(2H, s) 6.97(1H, s), 7.57(1H, d, J=8.8Hz) 7.92(1H, dd, J=8.8Hz, 2.0Hz) 8.61(1H, d, J=2.0Hz), 9.26(1H, t, J=5.6Hz)	
374	F	Cl	192-193	80	332(M+1)+	δ (DMSO-d_6) ; 4.65(2H, d, J=5.6Hz), 5.99(2H, s), 6.87(2H, s) 6.97(1H, s), 7.71(2H, m), 8.17(1H, m) 9.14(1H, t, J=5.6Hz)	
375	Br		239-240	80	513(M+1)+	δ (DMSO-d_6) ; 1.17(3H, t, J=7.2Hz), 1.56(2H, m), 1.94(2H, m) 2.72(1H, m), 3.3(2H, m), 4.06(2H, q, J=7.2Hz) 4.49(2H, m), 4.64(2H, d, J=6.0Hz), 5.95(2H, s) 6.83(1H, d, J=8.0Hz) 6.87(1H, dd, J=8.0Hz, 1.6Hz) 6.97(1H, d, J=1.6Hz), 7.80(1H, d, J=8.8Hz) 7.91(1H, dd, J=8.8Hz, 2.0Hz) 8.60(1H, d, J=2.0Hz), 10.10(1H, brs) 12.22(1H, brs)	hydrochloride

Table 42



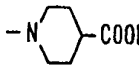
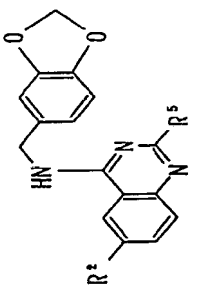
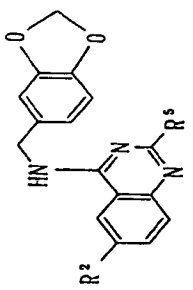
Ex.	R^2	R^5	m.p. (℃)	yield (%)	Mass	NMR	note
376	Br		209-210	96	485(M+1)⁺	δ (DMSO-d_6) : 1.38(2H, m), 1.79(2H, m), 2.46(1H, m) 2.95(2H, m), 4.53(2H, d, J=6.0Hz), 4.58(2H, m) 5.93(2H, s), 6.80(1H, d, J=8.0Hz) 6.83(1H, dd, J=8.0Hz, 1.6Hz) 6.91(1H, d, J=1.6Hz), 7.16(1H, d, J=9.2Hz) 7.55(1H, dd, J=9.2Hz, 2.4Hz) 8.24(1H, d, J=2.4Hz), 8.52(1H, t, J=6.0Hz) 12.13(1H, brs)	
377		Cl	200-201	36	397(M+1)⁺	δ ($CDCl_3$) : 1.62(2H, m), 1.73(4H, m), 3.21(4H, t, J=5.4Hz) 4.76(2H, d, J=5.2Hz), 5.80(1H, t, J=5.2Hz) 5.97(2H, s), 6.76(1H, d, J=2.4Hz) 6.81(1H, d, J=8.0Hz) 6.88(1H, dd, J=8.0Hz, 1.2Hz) 6.91(1H, d, J=1.2Hz) 7.48(1H, dd, J=9.2Hz, 2.4Hz) 7.66(1H, d, J=9.2Hz)	

Table 4 3



Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
378		Cl	226-227 (decomp)	94	357(M+1)'	δ (DMSO-d_6) : 2.99(6H, s), 4.63(2H, d, J=6.0Hz), 5.96(2H, s) 6.84(2H, s), 6.93(1H, s), 7.20(1H, d, J=2.8Hz) 7.37(1H, dd, J=9.2Hz, 2.8Hz) 7.46(1H, d, J=9.2Hz), 8.84(1H, t, J=6.0Hz)	
379	Cl		183-185	86	498(M+1)	δ (DMSO-d_6) : 2.43(2H, t, J=6.4Hz), 2.56(2H, t, J=6.4Hz) 3.46(4H, brs), 3.71(2H, brs), 3.77(2H, brs) 4.56(2H, d, J=5.6Hz), 5.95(2H, s) 6.83(1H, d, J=8.0Hz), 6.86(1H, d, J=8.0Hz) 6.94(1H, s), 7.27(1H, d, J=8.8Hz) 7.50(1H, dd, J=8.8Hz, 2.0Hz) 8.16(1H, d, J=2.0Hz), 8.61(1H, t, J=5.6Hz)	

Table 44



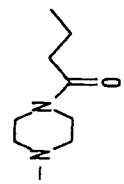
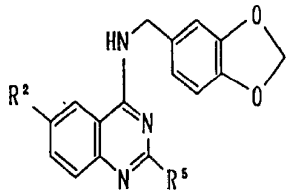
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
380	Cl		193-195	85	484(M+1)	δ (DMSO-d_6) : 3.44(6H, m), 3.73(2H, m), 3.78(2H, m) 4.56(2H, d, J=5.6Hz), 5.93(2H, s) 6.83(1H, d, J=8.0Hz), 6.85(1H, d, J=8.0Hz) 6.94(1H, s), 7.27(1H, d, J=8.8Hz) 7.50(1H, dd, J=8.8Hz, 2.0Hz) 8.16(1H, d, J=2.0Hz), 8.61(1H, t, J=5.6Hz)	
381	Cl		204-205	62	468(M+1)	δ ($CDCl_3$) : 1.00(3H, t, J=7.6Hz) 1.70(2H, sextet, J=7.6Hz) 2.36(2H, t, J=7.6Hz), 3.54(2H, brs) 3.69(2H, t, J=4.8Hz), 3.89(2H, t, J=4.8Hz) 3.92(2H, brs), 4.68(2H, d, J=5.2Hz) 5.65(1H, brs), 5.97(2H, s) 6.80(1H, d, J=8.0Hz) 6.84(1H, dd, J=8.0Hz, 0.8Hz) 6.87(1H, d, J=0.8Hz), 7.40(1H, m), 7.46(1H, m) 7.48(1H, m)	

Table 4 5



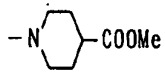
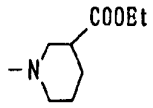
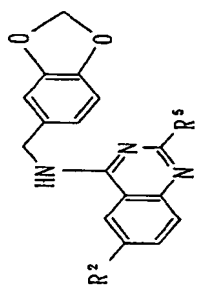
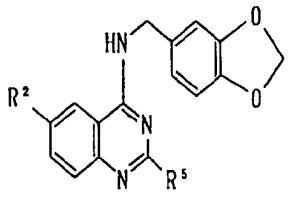
Ex.	R^2	R^5	m.p. (℃)	yield (%)	Mass	NMR	note
382	Cl		233-234	93	455(M+1)$^+$	δ(DMSO-d_6) ; 1.58(2H,m), 1.95(2H,m), 2.75(1H,m) 3.3(2H,m), 3.61(3H,s), 4.46(2H,m) 4.65(2H,d,J=5.6Hz), 5.96(2H,s) 6.84(1H,d,J=8.0Hz) 6.87(1H,dd,J=8.0Hz,1.2Hz) 6.97(1H,d,J=1.2Hz), 7.78(1H,brd,J=8.8Hz) 7.81(1H,brd,J=8.8Hz), 8.45(1H,brs) 10.05(1H,brs), 12.05(1H,brs)	hydrochloride
383	Cl		amorphous	99	469(M+1)$^+$	δ($CDCl_3$) ; 1.25(3H,t,J=7.2Hz), 1.54(1H,m), 1.70(1H,m) 1.78(1H,m), 2.11(1H,m), 2.52(1H,m), 2.98(1H,m), 3.14(1H,m), 4.15(2H,q,J=7.2Hz) 4.66(2H,m), 4.73(1H,m), 4.98(1H,m) 5.61(1H,brt), 5.95(2H,s) 6.78(1H,d,J=8.0Hz) 6.85(1H,dd,J=8.0Hz,1.6Hz) 6.88(1H,d,J=1.6Hz), 7.37-7.44(3H,m)	

Table 46



Ex.	R²	R⁵	m.p. (°C)	yield (%)	Mass	NMR	note
384	Cl		275-276 (decomp)	98	441(M+1)⁺	δ (DMSO-d₆) ; 1.34(1H, m), 1.56(1H, m), 1.65(1H, m) 1.97(1H, m), 2.28(1H, m), 2.85(1H, m) 2.95(1H, m), 4.53(2H, m), 4.57(1H, m) 4.81(1H, m), 5.93(2H, s), 6.78(1H, d, J=8.0Hz) 6.84(1H, dd, J=8.0Hz, 1.6Hz) 6.91(1H, d, J=1.6Hz), 7.24(1H, d, J=8.8Hz) 7.45(1H, dd, J=8.8Hz, 2.4Hz) 8.12(1H, d, J=2.4Hz), 8.55(1H, brs)	
385	Cl	-CN	198-199	35	339(M+1)⁺	δ (CDCl₃) ; 3.18(1H, br), 4.75(2H, d, J=5.2Hz) 5.97(2H, s), 6.17(1H, br) 6.81(1H, d, J=8.4Hz) 6.87(1H, dt, J=8.4Hz, 1.6Hz) 6.88(1H, d, J=1.6Hz), 7.72(1H, d, J=2.0Hz) 7.75(1H, dd, J=8.8Hz, 2.0Hz) 7.85(1H, d, J=2.0Hz)	

Table 47



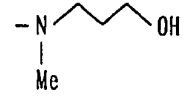
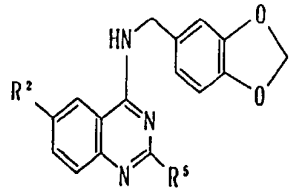
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
386	MeS	H	174-175	83	326(M+H)$^+$	δ(CDCl$_3$) : 2.59(3H, s), 4.79(2H, d, J=5.6Hz) 5.93(2H, s), 6.77(1H, d, J=8.0Hz) 6.89(1H, d, J=8.0Hz), 6.94(1H, s) 7.62(1H, dd, J=8.8Hz, 2.0Hz) 7.75(1H, d, J=8.8Hz), 7.97(1H, d, J=2.0Hz) 8.10(1H, brs), 8.56(1H, s)	
387	O ↑ -S-Me	H	154-155	80	342(M+H)$^+$	δ(CDCl$_3$) : 2.75(3H, s), 4.80(2H, d, J=5.2Hz) 5.96(2H, s), 6.80(1H, d, J=8.0Hz) 6.89(1H, d, J=8.0Hz), 6.91(1H, s) 7.06(1H, brs), 7.64(1H, d, J=8.8Hz) 7.98(1H, d, J=8.8Hz), 8.43(1H, s), 8.74(1H, s)	
388	Cl		154-155	71	401(M+1)$^+$	δ(DMSO-d$_6$) : 1.68(2H, m), 3.11(3H, s), 3.40(2H, t, J=6.2Hz) 3.65(2H, t, J=7.0Hz), 4.60(2H, d, J=5.6Hz) 6.83(1H, d, J=7.6Hz) 6.87(1H, dd, J=7.6Hz, 1.2Hz) 6.95(1H, d, J=1.2Hz), 7.31(1H, br) 7.52(1H, br), 8.19(1H, br)	

Table 4 8



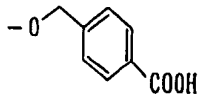
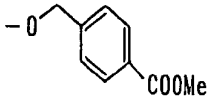
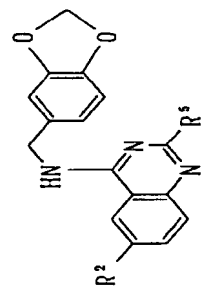
Ex.	R^2	R^5	m.p. (℃)	yield (%)	Mass	NMR	note
389	Cl	Cl	194-195 (decomp)	48	334($M+1)^+$	δ (DMSO-d_6) ; 6.04(2H, s), 6.95(1H, d, J=8.4Hz) 7.11(1H, dd, J=8.4Hz, 2.0Hz) 7.38(1H, d, J=2.0Hz), 7.69(1H, d, J=8.8Hz) 7.86(1H, dd, J=8.8Hz, 2.4Hz) 8.66(1H, d, J=2.4Hz), 10.13(1H, s)	
390	CN		298-300 (decomp)	29	455(MH^+)	δ (DMSO-d_6) ; 4.62(2H, d, J=5.6Hz), 5.47(2H, s), 5.45(2H, s) 6.81-6.82(2H, m), 6.90(1H, s) 7.51(2H, d, J=8.0Hz), 7.57(1H, d, J=8.8Hz) 7.90(2H, d, J=8.0Hz) 7.96(1H, dd, J=8.8Hz, 2.0Hz) 8.79(1H, d, J=2.0Hz), 9.10(1H, brt, J=5.1Hz)	
391	CN		176-179	35	469(MH^+)	δ ($CDCl_3$) ; 3.92(3H, s), 4.74(2H, d, J=5.2Hz), 5.58(2H, s) 5.92-5.99(1H, m), 5.99(2H, s) 6.60-6.69(3H, m), 7.57(2H, d, J=8.0Hz) 7.70(1H, d, J=8.8Hz) 7.80(1H, dd, J=8.8Hz, 1.6Hz) 7.95(1H, d, J=1.6Hz), 8.03(2H, d, J=8.0Hz)	

Table 49



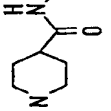
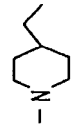
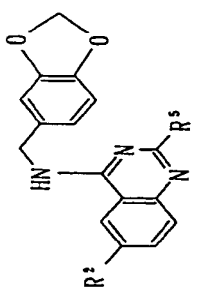
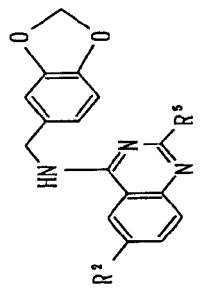
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
392	Cl		230 (decomp)	51		δ (DMSO-d_6) : 1.39(2H, m), 1.69(2H, m), 2.31(1H, m) 2.54(2H, t, J=7.2Hz), 2.82(2H, m) 3.31(2H, m), 4.56(2H, d, J=5.6Hz) 4.74(2H, m), 5.96(2H, s), 6.83(1H, d, J=8.0Hz) 6.86(1H, dd, J=8.0Hz, 1.6Hz) 6.94(1H, d, J=1.6Hz), 7.26(1H, d, J=8.8Hz) 7.47(1H, dd, J=8.8Hz, 2.4Hz) 7.72(1H, t, J=5.6Hz), 8.14(1H, d, J=2.4Hz) 8.54(1H, t, J=5.6Hz)	
393	Cl		255-256	96	455(M+1)	δ (DMSO-d_6) : 1.01(2H, m), 1.66(2H, brd, J=13.2Hz) 1.90(1H, brs), 2.12(2H, d, J=7.2Hz) 2.79(2H, brt, J=12.0Hz) 4.53(2H, d, J=5.6Hz), 4.71(2H, brd, J=13.2Hz) 5.94(2H, s), 6.82(2H, m), 6.92(1H, s) 7.22(1H, d, J=8.8Hz) 7.45(1H, dd, J=8.8Hz, 2.4Hz) 8.11(1H, d, J=2.4Hz), 8.51(1H, t, J=5.6Hz)	

Table 50



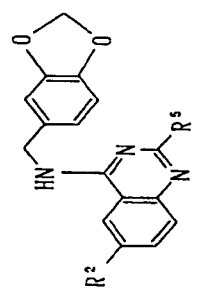
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
394	Cl		222-223	13	371(M+1)	δ (DMSO-d_6) : 3.54(2H, s), 4.66(2H, d, J=5.7Hz) 5.97(2H, s), 6.84(1H, d, J=7.9Hz) 6.90(1H, dd, J=7.9Hz, 1.6Hz) 6.98(2H, brs, d, J=1.6Hz), 7.43(1H, brs) 7.66(1H, d, J=9.0Hz) 7.76(1H, dd, J=9.0Hz, 3.2Hz) 8.40(1H, d, J=2.2Hz), 8.77(1H, t, J=5.7Hz)	
395	Cl		176-177	54	463(M+1)	δ (DMSO-d_6) : 4.39(2H, d, J=6.0Hz), 4.55(2H, d, J=5.6Hz) 5.93(4H, d, J=8.0Hz), 6.77(5H, m) 6.80(1H, br), 7.20(2H, br) 7.45(1H, dd, J=8.8Hz, 0.8Hz) 8.11(1H, d, J=2.4Hz), 8.38(1H, br)	

Table 5 1



Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
396	CN		176-179	35	469(MH^+)	δ ($CDCl_3$) : 3.92(3H, s), 4.74(2H, d, J=5.2Hz), 5.58(2H, s) 5.92-5.99(1H, m), 5.98(2H, s), 6.60-6.69(3H, m), 7.57(2H, d, J=8.0Hz) 7.70(1H, d, J=8.8Hz) 7.80(1H, dd, J=8.8Hz, 1.6Hz) 7.95(1H, d, J=1.6Hz), 8.03(2H, d, J=8.0Hz)	
397	CN		298-300 (decomp)	29	455(MH^+)	δ ($DMSO-d_6$) : 4.62(2H, d, J=5.6Hz), 5.47(2H, s), 5.45(2H, s) 6.81-6.82(2H, m), 6.90(1H, s) 7.51(2H, d, J=8.0Hz), 7.57(1H, d, J=8.8Hz) 7.90(2H, d, J=8.0Hz) 7.91(1H, dd, J=8.8Hz, 2.0Hz) 8.79(1H, d, J=2.0Hz), 9.10(1H, brt, J=5.1Hz)	

Table 52



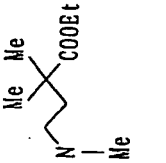
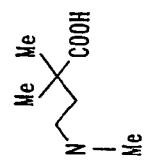
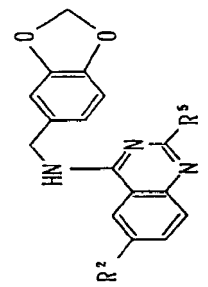
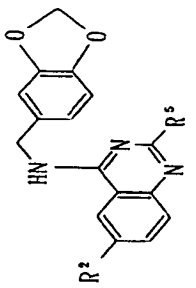
Ex.	R²	R⁵	m.p. (°C)	yield (%)	Mass	NMR	note
398	Cl		236-237	27	485(M+1)	δ (DMSO-d₆) ; 1.10(6H, s), 1.11(3H, t, J=7.2Hz) 1.76(2H, brs), 3.22(3H, s), 3.64(2H, m) 3.97(2H, q, J=7.2Hz), 4.71(2H, d, J=5.6Hz) 5.97(2H, s), 6.84(2H, s), 6.95(1H, s) 7.84(1H, dd, J=9.2Hz, 2.0Hz) 7.93(1H, d, J=9.2Hz), 8.53(1H, d, J=2.0Hz) 10.10(1H, brs), 11.95(1H, brs)	hydrochloride
399	Cl		240-241 (decomp)	78	457(M+1)	δ (DMSO-d₆) ; 1.086(6H, s), 1.66(2H, m), 3.03(3H, s) 3.54(2H, m), 4.59(2H, d, J=5.6Hz), 5.94(2H, s) 6.82(2H, s), 6.90(1H, s), 7.22(1H, d, J=9.2Hz) 7.45(1H, dd, J=9.2Hz, 2.0Hz) 8.12(1H, d, J=2.0Hz), 8.46(1H, brs)	

Table 5 3



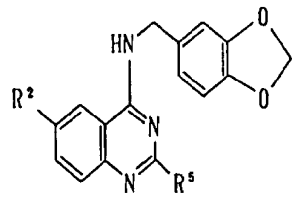
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
400	Cl		148-150	21	443(M+1)	δ (DMSO-d_6) : 1.05(3H, d, J=6.0Hz), 1.51(1H, m), 1.81(1H, m) 2.26(1H, m), 3.05(3H, s), 3.57(2H, m) 4.57(2H, d, J=5.6Hz), 5.94(2H, s), 6.82(2H, s) 6.91(1H, s), 7.23(1H, d, J=8.8Hz) 7.46(1H, dd, J=8.8Hz, 1.2Hz) 8.13(1H, d, J=1.2Hz), 8.49(1H, brs)	
401	Cl		180-182 (decomp)	80	485(MH^+)	δ ($CDCl_3$) : 2.85(2H, t, J=7.0Hz), 3.72-3.78(2H, m) 4.85(2H, d, J=5.2Hz), 5.84(2H, s) 6.35(1H, brt, J=5.4Hz), 6.66(1H, d, J=8.0Hz) 6.78(1H, dd, J=8.0Hz, 1.6Hz) 6.82(1H, d, J=1.6Hz), 7.18-7.29(5H, m) 7.61(1H, dd, J=8.8Hz, 2.2Hz) 7.69-7.72(2H, m), 7.99(1H, br)	

Table 5 4



Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
402	Cl		169 (decomp)	62	470(MH⁺)	δ (DMSO-d_6) : 3.77-3.81(2H, m), 4.76(2H, t, J=5.2Hz) 4.92(2H, d, J=6.0Hz), 5.97(2H, s) 6.86(1H, d, J=8.0Hz) 6.97(1H, dd, J=8.0Hz, 2.0Hz) 7.05(1H, d, J=2.0Hz), 7.83(1H, d, J=8.8Hz) 7.92(1H, dd, J=8.8Hz, 2.4Hz) 8.56(1H, d, J=2.4Hz), 9.04(1H, t, J=6.0Hz) 9.4848(1H, t, J=6.0Hz)	
403	Cl		243-245 (decomp)	58	425(MH⁺)	δ (DMSO-d_6) : 3.44-3.48(2H, m), 3.56-3.60(2H, m) 4.37-4.51(3H, m), 5.94(2H, s) 6.83(1H, d, J=8.0Hz) 6.94(1H, dd, J=8.0Hz, 1.6Hz) 7.02(1H, d, J=1.6Hz), 7.80(1H, d, J=8.8Hz) 7.89(1H, dd, J=8.8Hz, 2.4Hz) 8.53(1H, d, J=2.4Hz), 9.20(1H, br)	

Table 5 5



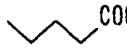
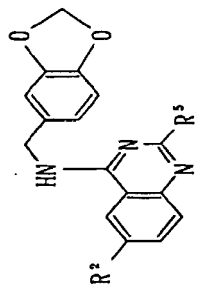
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
404	Cl		210 213 (decomp)		344(MH$^+$)	δ(DMSO-d_6) ; 4.41(2H, d, J=6.0Hz), 4.66(2H, d, J=5.6Hz) 4.84(1H, t, J=6.0Hz), 5.95(2H, s) 6.83(1H, d, J=7.6Hz) 6.86(1H, dd, J=7.6Hz, 1.6Hz) 6.97(1H, d, J=1.6Hz), 7.67(1H, d, J=8.8Hz) 7.75(1H, dd, J=8.8Hz, 2.4Hz) 8.40(1H, d, J=2.4Hz), 8.78(1H, t, J=5.6Hz)	
405	Cl		191- 192	97	400(M+1)	δ(DMSO-d_6) ; 1.97(2H, quintet, J=7.4Hz) 2.26(2H, t, J=7.4Hz), 2.72(2H, t, J=7.4Hz) 4.65(2H, d, J=5.7Hz), 5.97(2H, s) 6.83(1H, d, J=8.0Hz) 6.88(1H, dd, J=8.0Hz, 1.6Hz) 6.96(1H, d, J=1.6Hz), 7.63(1H, d, J=9.0Hz) 7.73(1H, dd, J=9.0Hz, 2.2Hz) 8.39(1H, d, J=2.2Hz), 8.72(1H, t, J=5.7Hz)	

Table 5 6

Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
406	CN		245-246	55	391(M+1)	δ (DMSO-d_6) : 1.98(2H, quintet, J=7.4Hz) 2.29(2H, t, J=7.4Hz), 2.75(2H, t, J=7.4Hz) 4.68(2H, d, J=5.7Hz), 5.97(2H, s) 6.85(1H, d, J=7.9Hz) 6.89(1H, dd, J=7.9Hz, 1.6Hz) 6.98(1H, d, J=8.6Hz), 7.72(1H, d, J=8.6Hz) 8.02(1H, dd, J=8.6Hz, 1.6Hz) 8.84(1H, d, J=1.6Hz), 8.96(1H, t, J=5.7Hz)	
407	Cl		201-202	99	386(M+1)	δ (DMSO-d_6) : 2.71(2H, t, J=7.1Hz), 2.96(2H, t, J=7.1Hz) 4.65(2H, d, J=5.7Hz), 5.97(2H, s) 6.85(1H, d, J=7.9Hz) 6.89(1H, dd, J=7.9Hz, 1.6Hz) 6.98(1H, d, J=1.6Hz), 7.62(1H, d, J=9.0Hz) 7.73(1H, dd, J=9.0Hz, 2.2Hz) 8.39(1H, d, J=3.2Hz), 8.73(1H, t, J=5.7Hz)	

Table 57



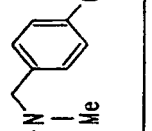
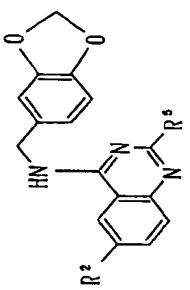
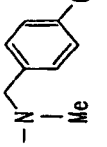
Ex.	R^2	R^5	m.p. (°C)	yield (%)	Mass	NMR	note
408	Cl		231-232 (decomp)	79	440(M+1)$^+$	δ (DMSO-d_6) : 1.40(2H, m), 1.71(2H, m), 2.34(1H, m) 2.82(2H, m), 4.56(2H, d, J=5.6Hz), 4.74(2H, m) 5.95(2H, s), 6.73(1H, brs) 6.82(1H, d, J=8.0Hz) 6.86(1H, dd, J=8.0Hz, 1.6Hz) 6.94(1H, d, J=1.6Hz), 7.25(1H, brs) 7.25(1H, d, J=8.8Hz) 7.47(1H, dd, J=8.8Hz, 2.4Hz) 8.14(1H, d, J=2.4Hz), 8.53(1H, brt, J=5.6Hz)	hydrochloride
409	Cl		215 (decomp)	81	505(MH$^+$)	δ (DMSO-d_6) : 1.27(3H, t, J=7.0Hz), 3.21(3H, s) 4.30(2H, q, J=7.0Hz), 4.55(2H, brs) 4.97(2H, s), 5.89(2H, s), 6.52-8.42(10H, m) 12.20(1H, brs)	

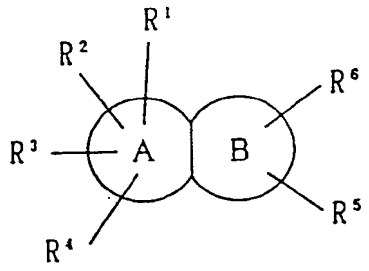
Table 58



Ex.	R²	R⁵	m.p. (°C)	yield (%)	Mass	NMR	note
410	Cl		279-280 (decomp)	91	477(MH⁺)	δ (DMSO-d_6) : 3.07(2H, s), 4.50(2H, brs), 4.81(2H, s) 5.89(2H, s), 6.51-6.88(3H, m) 7.22(2H, d, J=8.0Hz), 7.26(1H, d, J=9.2Hz) 7.48(1H, dd, J=9.2Hz, 2.4Hz) 7.80(2H, d, J=8.0Hz), 8.15(1H, d, J=2.4Hz) 8.58(1H, brs), 12.77(1H, brs)	

Claims

1. A nitrogenous heterocyclic compound represented by the following general formula (1) or a pharmacologically acceptable salt thereof:

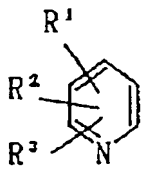


(1)

[in formula (1), ring A represents a benzene ring, a pyridine ring or a cyclohexane ring; ring B represents a pyridine ring, a pyrimidine ring, or an imidazole ring.

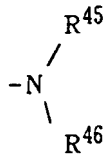
Provided that the ring A and the ring B are combined sharing two atoms and the atoms shared may be either a carbon atom or a nitrogen atom.

In the case where the ring A is a pyridine ring and that except the case where the ring B shares the nitrogen atom of this pyridine ring to combine therewith, the ring A is represented by



R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a lower alkyl group which may be substituted with a halogen atom, a cycloalkyl group which may be substituted, a lower alkoxy group, a hydroxyalkyl group, a nitro group, a cyano group, an acylamino group, a carboxyl group which may be protected, a group represented by the formula

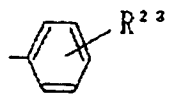
(wherein R^7 represents a lower alkyl group, and n represents 0 or an integer of 1 to 2), or a group represented by the formula



(wherein R^{45} and R^{46}, each of which may be the same or different from each other, represent each a hydrogen atom or a lower alkyl group; or R^{45} and R^{46} can form a ring which may contain another nitrogen atom or oxygen atom together with the nitrogen atom to which they are bonded with the proviso that this ring may be substituted); or, two of R^1, R^2, R^3 and R^4 may together form methylenedioxy, ethylenedioxy or a phenyl ring.

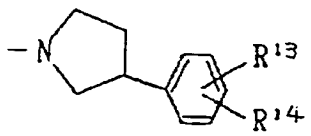
R^5 represents a hydrogen atom, a halogen atom, a hydroxyl group, a hydrazino group, a lower alkyl group, a cycloalkyl group which may be substituted, a lower alkoxy group, a lower alkenyl group, a carboxyalkyl group which may be protected, a carboxyalkenyl group which may be protected, a hydroxyalkyl group, a carboxyl group which may be protected, a group represented by the formula

(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula -O-R^9 (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group which may be substituted), a group represented by the formula

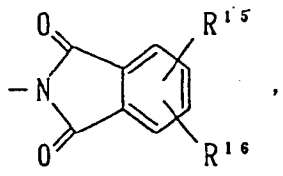


(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl group which may be substituted, a 1,4-benzdioxylalkyl group which may be substituted, a group represented by the formula -C(R^{24})=X [wherein X represents an oxygen atom, a sulfur atom or a group represented by the formula =N-R^{10} (wherein R^{10} represents a hydroxyl group, a cyano group or a carboxyalkyloxy group which may be protected); and R^{24} represents a hydrogen atom or a lower alkyl group], or a group represented by the formula -$NR^{11}R^{12}$ (wherein R^{11} and R^{12}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, an aminoalkyl group, a carboxyalkyl group which may be protected, an alkylcarbamoyl group, a carboxyalkylcarbamoyl group which may be protected, a heteroarylalkyl group which may be substituted, a 1,3-benzoxolylalkyl group or a 1,4-benzdioxylalkyl group; or, further, R^{11} and R^{12} can form a ring which may contain another nitrogen atom or oxygen atom together with a nitrogen atom to which they are bonded with the proviso that this ring may be substituted).

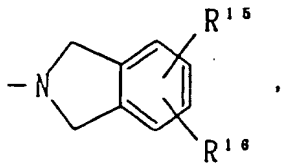
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



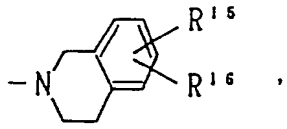
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



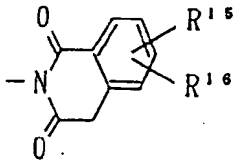
a group represented by the formula



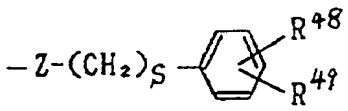
a group represented by the formula



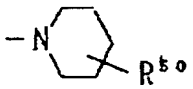
a group represented by the formula



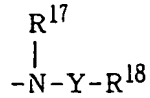
(in these formulas, R^{15} and R^{16}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidne-4-spiro-2'-dioxan-1-yl group, a group represented by the formula



(wherein R^{48} and R^{49}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{48} and R^{49} may together form methylenedioxy or ethylenedioxy; and Z represents a sulfur atom or an oxygen atom), a group represented by the formula



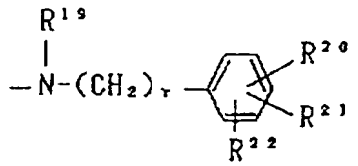
(wherein R^{50} represents a hydroxyl group, a halogen atom, a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a cyano group, a hydroxyalkyl group or a carboxyalkyl group), a group represented by the formula



[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented by

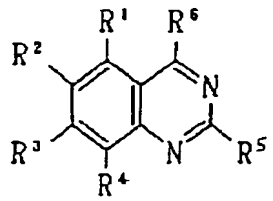
the formula

further, in the group represented by the formula $-(CH_2)_q-$, when q is an integer of 1 to 8, each carbon atom may have 1 to 2 substituent(s); and R^{18} represents a hydrogen atom, a hydroxyl group, a carboxyl group which may be protected, a cyano group, an acyl group, a heteroaryl group which may be substituted or a cycloalkyl group which may be substituted], or a group represented by the formula



(wherein R^{19} represents a hydrogen atom, a lower alkyl group, a lower alkoxyalkyl group, an acyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; R^{20}, R^{21} and R^{22}, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a lower alkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a lower alkenyl group, an acyl group, an acylamino group, an alkylsulfonylamino group, a hydroxyiminoalkyl group, an alkyloxycarbonylamino group, an alkyloxycarbonyloxy group or a heteroaryl group which may be substituted; or, further, two of R^{20}, R^{21} and R^{22} may together form a saturated or unsaturated ring which may contain a nitrogen atom, a sulfur atom or an oxygen atom; and r represents 0 or an integer of 1 to 8)].

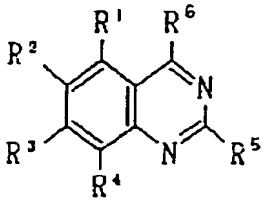
2. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 1, which is represented by the following general formula (2):



(2)

[in formula (2), R^1, R^2, R^3, R^4, R^5 and R^6 are the same as those in formula (1), respectively].

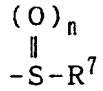
3. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 1, which is represented by the following general formula (I):



(I)

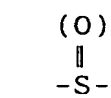
[in formula (I), R^1, R^2, R^3 and R^4, each of which may be the same or different from one another,

represent each a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group, a cyano group, an acylamino group, a carboxyl group which may be protected or a group represented by the formula

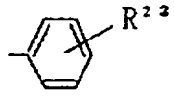


(wherein R^7 represents a lower alkyl group; and n represents 0 or an integer of 1 to 2), or two of R^1, R^2, R^3 and R^4 may together form methylenedioxy, ethylenedioxy or a phenyl ring.

R^5 represents a hydrogen atom, a halogen atom, a hydroxyl group, a hydrazino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a carboxyalkyl group which may be protected, a carboxyalkenyl group which may be protected, a hydroxyalkyl group, a carboxyl group which may be protected, a group represented by the formula

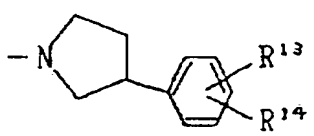


(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula $-O-R^9$ (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group), a group represented by the formula

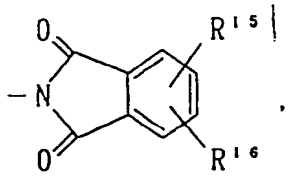


(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl group which may be substituted, a 1,4-benzdioxylalkyl group which may be substituted, a group represented by the formula $-C(R^{24})=X$ [wherein X represents an oxygen atom or a group represented by the formula $=N-R^{10}$ (wherein R^{10} represents a hydroxyl group or a carboxyalkyloxy group which may be protected); and R^{24} represents a hydrogen atom or a lower alkyl group], or a group represented by the formula $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, an aminoalkyl group, a carboxyalkyl group which may be protected, an alkylcarbamoyl group, a 1,3-benzoxolylalkyl group or a 1,4-benzdioxylalkyl group; or, further, R^{11} and R^{12} can form a ring which may contain another nitrogen atom or oxygen atom together with a nitrogen atom to which they are bonded with the proviso that this ring may be substituted).

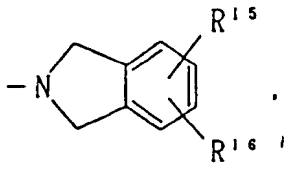
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



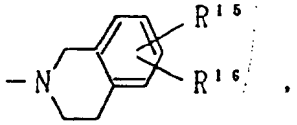
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



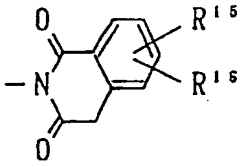
a group represented by the formula



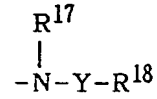
a group represented by the formula



a group represented by the formula



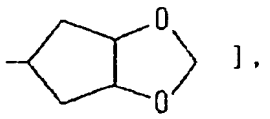
(in these formulas, R^{15} and R^{16} represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidne-4-spiro-2'-dioxan-1-yl group or a group represented by the formula



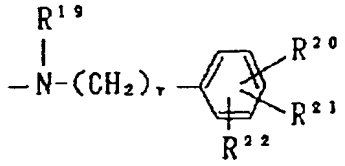
[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented by the formula

further, in the group represented by the formula $-(CH_2)_q-$, when q is an integer of 1 to 8, each carbon atom may have 1 to 2 substituent(s); and R^{18} represents a hydrogen atom, a hydroxyl group, a

carboxyl group which may be protected, a cyano group, an acyl group, a heteroaryl group which may be substituted or a group represented by the formula

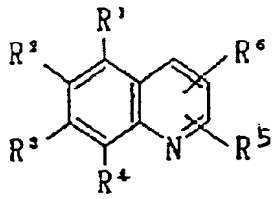


or a group represented by the formula



(wherein R^{19} represents a hydrogen atom, a lower alkyl group, a lower alkoxyalkyl group, an acyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; R^{20}, R^{21} and R^{22}, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a lower alkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a lower alkenyl group, an acyl group, an acylamino group, an alkylsulfonylamino group, a hydroxyiminoalkyl group, an alkyloxy-carbonylamino group, an alkyloxycarbonyloxy group or a heteroaryl group which may be substituted; or, two of R^{20}, R^{21} and R^{22} may together form a saturated or unsaturated ring which may contain a nitrogen atom, a sulfur atom or an oxygen atom; and r represents 0 or an integer of 1 to 8)].

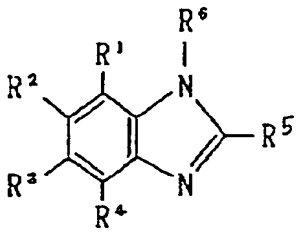
4. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 1, which is represented by the following general formula (3):



(3)

[in formula (3), R^1, R^2, R^3, R^4, R^5 and R^6 are the same as those in formula (1), respectively].

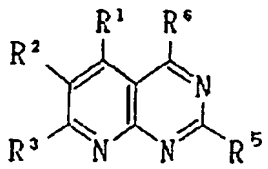
5. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 1, which is represented by the following general formula (4):



(4)

[in formula (4), R^1, R^2, R^3, R^4, R^5 and R^6 are the same as those in formula (1), respectively].

6. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 1, which is represented by the following general formula (5):



(5)

[in formula (5), R^1, R^2, R^3, R^5 and R^6 are the same as those in formula (1), respectively].

7. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 1, wherein R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, represent each a hydrogen atom, a cyano group, a halogen atom or a lower alkoxy group in the above general formula (1).

8. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 1, wherein one of R^1, R^2, R^3 and R^4 is a cyano group, a chlorine atom or a methoxy group in the above general formula (1).

9. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, represent each a hydrogen atom, a cyano group, a halogen atom or a lower alkoxy group in the above general formula (I).

10. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein one of R^1, R^2, R^3 and R^4 is a cyano group, a chlorine atom or a methoxy group in the above general formula (I).

11. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^2 is a cyano group in the above general formula (I).

12. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^2 is a halogen atom in the above general formula (I).

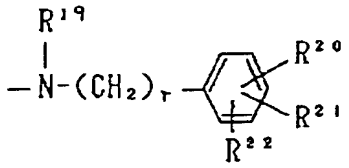
13. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^2 is a chlorine atom in the above general formula (I).

14. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^2 is a lower alkoxy group in the above general formula (I).

15. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^2 is a methoxy group in the above general formula (I).

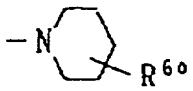
16. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^5 is a group represented by the formula $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, an aminoalkyl group, a carboxyalkyl group which may be protected, an alkylcarbamoyl group, a 1,3-benzdioxolylalkyl group or a 1,4-benzdioxylalkyl group, or further R^{11} and R^{12} may form a ring which may contain another nitrogen atom and/or oxygen atom together with the nitrogen atom to which they are bonded, and which may be substituted) in the above general formula (I).

17. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^6 is a group represented by the formula



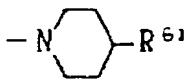
(wherein R^{19} represents a hydrogen atom, a lower alkyl group, a lower alkoxyalkyl group, an acyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; R^{20}, R^{21} and R^{22}, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a hydroxy group, an amino group, a nitro group, a lower alkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a lower alkenyl group, an acyl group, an acylamino group, an alkylsulfonylamino group, a hydroxyiminoalkyl group, an alkyloxycarbonylamino group, an alkyloxycarbonyloxy group or a heteroaryl group which may be substituted, or two of R^{20}, R^{21} and R^{22} may together form a saturated or unsaturated ring which may contain a nitrogen atom, a sulfur atom or an oxygen atom; and r represents 0 or an integer of 1 to 8) in the above general formula (I).

18. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^5 is a group represented by the formula



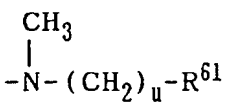
(wherein R^{60} represents a hydroxyl group which may be protected, a cyano group, a halogen atom, a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a hydroxyalkyl group, a carboxyalkyl group or a heteroaryl group) in the above general formula (I).

19. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^5 is a group represented by the formula:



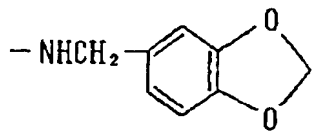
(wherein R^{61} represents a carboxyl group which may be protected or a heteroaryl group) in the above general formula (I).

20. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^5 is a group represented by the formula



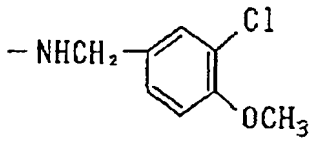
(wherein R^{61} represents a carboxyl group which may be protected; and u represents 3 or 4) in the above general formula (I).

21. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^6 is a group represented by the formula



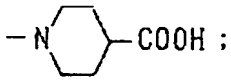
in the above general formula (I).

22. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^6 is a group represented by the formula

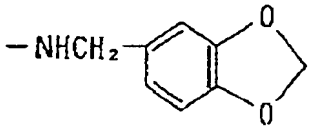


in the above general formula (I).

23. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^1, R^3 and R^4 are hydrogen atoms; R^2 is a chlorine atom; R^5 is a group represented by the formula

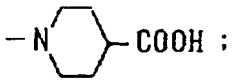


and R^6 is a group represented by the formula

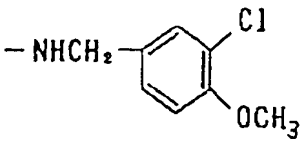


in the above general formula (I).

24. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^1, R^3 and R^4 are hydrogen atoms; R^2 is a cyano group; R^5 is a group represented by the formula

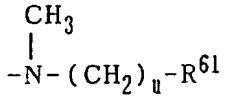


and R^6 is a group represented by the formula

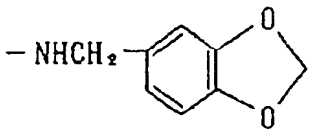


in the above general formula (I).

25. The nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claim 3, wherein R^1, R^3 and R^4 are hydrogen atoms; R^2 is a cyano group; R^5 is a group represented by the formula



(wherein R^{61} represents a carboxyl group which may be protected); and R^6 is a group represented by the formula



in the above general formula (I).

26. A preventive or therapeutic agent for diseases for which a phosphodiesterase-inhibitory action is efficacious, which contains the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 as the active ingredient.

27. A preventive or therapeutic agent for diseases for which a cyclic-GMP phosphodiesterase-inhibitory action is efficacious, which contains the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 as the active ingredient.

28. A preventive or therapeutic agent for ischemic heart diseases, which contains the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 as the active ingredient.

29. A preventive or therapeutic agent for angina pectoris, which contains the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 as the active ingredient.

30. A preventive or therapeutic agent for hypertension, which contains the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 as the active ingredient.

31. A preventive or therapeutic agent for heart failure, which contains the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 as the active ingredient.

32. A preventive or therapeutic agent for asthoma, which contains the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 as the active ingredient.

33. A drug composition comprising a therapeutic effective amount of the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3, and a pharmacologically acceptable filler.

34. A use of the nitrogenous heterocyclic compound or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 to prepare a therapeutic agent for diseases for which phosphodiesterage-inhibitory action is efficacious.

35. A treating method for a disease which comprises administering a therapeutic effective amount of the nitrogenous heterocyclic compound and/or the pharmacologically acceptable salt thereof as set forth in claims 1 or 3 to a patient suffering from a disease for which phosphodiesterase-inhibitory action is efficacious.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/01258

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl[5] C07D215/00, 215/00, 235/00, 239/72, 239/84, 239/94, 239/95, A61K31/47, 31/505

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	C07D215/00, C07D235/00, 239/72-95, A61K31/47, 31/505

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	JP, A, 57-171973 (Rhone-Poulene Sant), October 22, 1982 (22. 10. 82), & EP, A, 56766 & US, A, 4421920	1, 4, 33, 34
X	JP, A, 59-33264 (Pfizer Corp.), February 23, 1984 (23. 02. 84), (Family: none)	1, 4, 26-31, 33, 34
X	JP, A, 53-71088 (Abbot Laboratory), June 24, 1978 (24. 06. 78), & US, A, 4093726 & GB, A, 1583357	1, 5, 30, 33 34
X	JP, A, 58-79983 (Kanebo, Ltd.), May 13, 1983 (13. 05. 83), & EP, A, 79545 & US, A, 4430343	1, 5, 33, 34
X	JP, A, 63-96174 (Beringer Mannheim GmbH.), April 27, 1988 (27. 04. 88), & DE, A, 3634066 & EP, A, 266558 & US, A, 4882342	1, 5, 26-31, 33, 34
X	JP, A, 64-74 (Otsuka Pharmaceutical Factory, Inc.),	1, 5, 26-34

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
November 16, 1992 (16. 11. 92)	December 8, 1992 (08. 12. 92)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	January 5, 1989 (05. 01. 89), (Family: none)	
X	JP, A, 55-160776 (Warnar-Lambert Co.), December 13, 1980 (13. 12. 80), & EP, A, 18151 & US, A, 4271164	1, 6, 30, 33, 34
X	JP, A, 61-167688 (Bayer AG.), July 29, 1986 (29. 07. 86), & EP, A, 189045 & US, A, 4621082	1, 6, 26-31, 33, 34
X	JP, A, 63-216884 (The Wellcome Foundation Ltd.), September 9, 1988 (09. 09. 88),	1, 6, 33, 34

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 35 , because they relate to subject matter not required to be searched by this Authority, namely:

Claim 35 pertains to a medical treatment of the human body by curing.

2. [ ] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	& EP, A, 279565 & US, A, 4618759	
X	JP, A, 61-33185 (Pfizer Corp.), February 17, 1986 (17. 02. 86), & EP, A, 168151 & US, A, 4647565	1-3, 7-31, 33, 34
X	JP, A, 61-140568 (Mitsui Petrochemical Industries, Ltd. and another), June 27, 1986 (27. 06. 86), & EP, A, 188094 & US, A, 4734418	1-3, 7-25, 30, 33, 34
X	JP, A, 3-17068 (Smithkline Beecham Intercredit B.V.), January 25, 1991 (25. 01. 91),	1-3, 7-25, 33, 34

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	& US, A, 5064833 & EP, A, 404322	
X	J. Med. Chem., 28(1), 12-17 (1985)	1-3, 7-34

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.